benzoates. This greater activity is particularly noticeable in the case of the ethyl esters, for 1 and 3 show quite marked anesthetic effect on the rabbit's cornea while the corresponding benzoates are without any such effect. The 4-methylpiperidino derivatives seem appreciably more active than the isomeric 3-methyl- and 2-methylpiperidino derivatives. With the exception of γ-3-methylpiperidinopropyl cinnamate, the toxicities of the members of the cinnamate series are, in general, greater than those of the benzoates.

Summary

1. The methylpiperidino-ethyl and propyl cinnamates have been prepared and described.

2. A comparison of their pharmacological properties with those of the corresponding benzoates is given.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

ATTEMPTED CORRELATIONS OF CONSTITUTION WITH SWEET TASTE IN THE FURAN SERIES. THE VERY HIGH SWEETENING POWER OF 5-BENZYL-2-FURFURALDOXIME

BY HENRY GILMAN AND J. B. DICKEY

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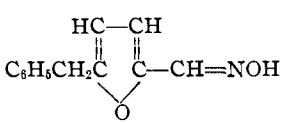
Introduction

In extension of studies[1] concerned with some correlations of constitution with sweet taste in the furan series we have come upon a compound which is sweeter than saccharin. The compound is *syn*-5-benzyl-2-furfuraldoxime



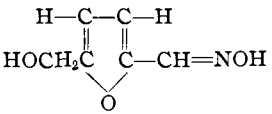
and it was found to be 690 times sweeter than sugar. The *anti*-form of this oxime is about 100 times sweeter than sugar.

These two isomers were prepared earlier by Fenton and Robinson,[2] but apparently they overlooked the sweet taste of the compounds.

It is interesting to note that both the *syn*- and the *anti*-oximes of 5-hydroxymethyl-2-furfural

[1] (a) Gilman and Hewlett, *Iowa State Coll. J. of Sci.*, **3**, 27 (1929). This article contains leading references to pertinent papers and standard texts. We omitted in that paper reference to (b) Asahina and Fujita, *J. Pharm. Soc. Japan*, **490**, 1084 (1922); [*C. A.*, **17**, 2578 (1923)].

[2] Fenton and Robinson, *J. Chem. Soc.*, **95**, 1334 (1909).



are without sweet taste. This would hardly have been predicted. However, despite an increasing literature on taste and constitution, too little is known about the subject to warrant broad and inflexible generalizations. This is particularly true in connection with the interesting and important biological relationships of isomers, especially geometrical and optical isomers. For example, the *anti*-oxime of perilla aldehyde is the sweetest compound so far described, and its *syn*-form is without a sweet taste; the two oximes of furfural[1] appear to be equally sweet; the *syn*-oxime of furylacetaldehyde is *one-half* as sweet as its *anti*-isomer;[3] and our *syn*-oxime of 2-benzyl-furfural is about *seven* times sweeter than its *anti*-form. Of course, there is always the possibility that what is called the *syn*-form of some geometrical isomers may in reality be the *trans* form and *vice versa*.

Experimental Part

5-Chloromethyl-2-furfural, $ClCH_2(C_4H_2O)CHO$.—The 5-chloromethyl-2-furfural was prepared in accordance with the directions of Fischer and Neyman[4] from cane sugar and concd. hydrochloric acid. To prevent the emulsion described by them, the solution, after the addition of sodium carbonate, was filtered and the solid removed in this manner was washed with water to recover any chloromethyl furfural. The average yield of a number of preparations starting with 200 g. of sugar was 11.2%, and the maximum yield was 17%. The range of yield reported by Fischer and Neyman[4] was 22–25%, and the yield obtained by Middendorp[5] was 11% from one kilogram of sugar. All calculations are based on the weight of the sugar taken.

5-Hydroxymethyl-2-furfural, $HOCH_2(C_4H_2O)CHO$.—Twenty-one grams (0.145 mole) of crude chloromethyl-furfural was poured into 750 cc. of boiling water and boiled for fifteen minutes. The yellowish solution containing some tar was cooled and then extracted 15 times with a total of one liter of ether until the solution was essentially colorless. The aqueous solution was salted out by saturating with hydrated sodium sulfate. The ether extract was then dried over anhydrous sodium sulfate. The yield was 45% in one experiment and 66.6% in another where the number of ether extractions was increased to 25.[6]

The two oximes of 5-hydroxymethyl-2-furfural were prepared in the manner described by Kiermayer.[7] A 62.5% yield of pure oxime was obtained from 10 g. of the crude aldehyde.

[3] Ref. 1b. It is interesting to know, apart from furan types, that Goldschmidt, *Ber.*, **23,** 2163 (1890), reported *anti*-anisaldoxime as being intensely sweet, whereas the *syn*-form is tasteless. There is a like difference with the *p*-nitrobenzaldoximes [see Cohn, "Die Organischen Geschmacksstoffe," Berlin, **1914**].

[4] Fischer and Neyman, *Ber.*, **47,** 974 (1914).

[5] Middendorp, *Rec. trav. chim.*, **38,** 1 (1919).

[6] When the hydrolysis was effected in boiling water containing powdered barium carbonate [Cooper and Nuttall, *J. Chem. Soc.*, **99,** 1193 (1911)] there appeared to be more decomposition and the yield was 30%.

[7] Kiermayer, *Chem.-Ztg.*, **19,** 1003 (1895).

5-Benzyl-2-furfuraldoxime, $C_6H_5CH_2(C_4H_2O)CH{=}NOH$.—5-Benzyl-2-furfural was prepared by the reaction of chloromethyl-furfural, benzene and aluminum chloride.[2] In addition to the two oximes which were prepared by a standard procedure,[2] we also prepared the known phenylhydrazone[2] in order further to identify our aldehyde.

Relative Sweetening Powers.—The method of evaluating the sweetness of the several oximes was that described earlier by Gilman and Hewlett.[1] The tests were carried out by a number of people.[8] By a method of cross-checking used previously by Gilman and Hewlett,[1] the currently accepted values for saccharin[9] and dulcin were first checked within the experimental error for such studies. The solutions of the sparingly soluble *syn-* and *anti*-benzyl-furfuraldoximes were made up by dissolving 0.02 and 0.04 g., respectively, of each of the oximes in 819 cc. of distilled water. The standard sugar solution (of 1.8% concentration by weight) was prepared from 0.0892 g. of sugar in 5 g. of water. The saccharin and dulcin solutions were of the same concentration as the *syn*-benzyl-furfuraldoxime.

It was found that the *syn*-isomer is about 690 times sweeter than sugar, and the *anti*-isomer about 100 times sweeter than sugar. By direct comparison it was found that the *syn*-isomer is slightly sweeter than saccharin. Aqueous alcoholic solutions of the oximes are decidedly sweet.

It is interesting to note that with both isomers there is an apparent lag or induction period before the sweet taste becomes apparent. This time interval between no taste and a sweet taste is very short but distinct. Once the sweet taste becomes apparent it rapidly increases to a maximum. Later the sweet taste is replaced by a pungent taste. At their respective maxima the sweet taste of the *anti*-form is less pleasant than that of the *syn*-form.

Studies are in progress on the introduction of water solubilizing groups with the hope of retaining the sweetening characteristics of the benzyl-furfuraldoximes.

The 5-hydroxymethyl-2-furfuraldoximes were devoid of sweet taste.[10]

Summary

It has been found that *syn*-5-benzyl-2-furfuraldoxime is sweeter than saccharin and that it is also about seven times sweeter than its *anti-*

[8] The authors are grateful for assistance rendered by Drs. P. Mabel Nelson and Louise Jennison Peet of the Department of Foods and Nutrition; to 12 students in one of their classes in foods; and to Dr. B. W. Hammer of Dairy Bacteriology. All of these individuals have had experience in detecting and differentiating tastes in a variety of foods. In addition, we wish to thank 7 graduate students in Chemistry who helped with the several taste tests.

[9] Magidson and Gorbatschow, *Ber.*, **56**, 1810 (1923). Also, Paul, *Chem.-Ztg.*, **4**, 38 (1921).

[10] Erdmann, *Ber.*, **43**, 2391 (1910), reported that the corresponding hydroxymethyl-furfural has a sharp, burning taste.

isomer. Attention is directed to an apparent lack of correlation between geometrical isomers of the furan series and their sweet taste.

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[CONTRIBUTION FROM THE RESEARCH LABORATORY, THE UPJOHN COMPANY]

THE STEROLS OF ERGOT

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In recent years considerable literature has developed about the chemistry of the ergosterol of yeast and its accompanying sterols, though but one paper[1] on the chemistry of the ergosterol of ergot since the original work by Tanret[2] has come to our attention. In this paper Rosenheim and Webster report on the irradiation of a "fungisterol" which, however, differs widely from that described by Tanret, and at the same time differs from any of the sterols accompanying the ergosterol of yeast as described by Wieland and Asano.[3]

Having at hand a considerable quantity of the ergosterol from ergot, it seemed desirable to us (1) to repeat and confirm if possible Tanret's isolation of fungisterol, and (2) to prepare a number of derivatives of our ergosterol, some previously described and some new, with a view to establishing more rigorously, or to disestablish, the complete chemical identity of the sterol from the two sources. That differences might be expected is indicated by the experience of Heilbron, Sexton and Spring,[4] who found two different specimens of ergosterol from yeast which behaved quite differently upon hydrogenation. In this paper we present our work on the fractionation of the ergot sterols; we hope in subsequent papers to report on a number of derivatives of the ergosterol of ergot.

Experimental

Preparation of Ergosterol.—Spanish ergot was exhaustively extracted with benzene and, after recovery of the solvent, the residue boiled with an excess of 20% alcoholic potassium hydroxide. The unsaponifiable fraction was removed in the usual way, and crude ergosterol precipitated by the addition of petroleum ether (b. p. 60–80°) to the concentrated ether extract. The yield of this crude averaged 0.13% of the ergot used. When twice crystallized from ethyl alcohol, plates melting at 152–157° were obtained. Filtration of a chloroform solution of this material removed a small amount of amorphous substance and subsequent crystallization of the soluble portion raised the melting point to 160–162°. Acetylation, crystallization of the acetate from acetic acid, ethyl and methyl alcohols, and subsequent hydrolysis, failed to raise this. $[\alpha]_D$ varied from −112.2 to −100° in various runs, with the yield averaging about 60% of the crude.

[1] Rosenheim and Webster, *Biochem. J.*, **22**, 1426 (1928).

[2] Tanret, *Compt. rend.*, **108**, 98 (1889); *ibid.*, **147**, 75 (1908).

[3] Wieland and Asano, *Ann.*, **473**, 300 (1929).

[4] Heilbron, Sexton and Spring, *J. Chem. Soc.*, 926 (1929).