heated on a steam-cone for 1.5 hours and worked up as described for 2-benzylthio-1-nitrobutane (I). An attempt to distil the crude product at 0.2 mm. resulted in extensive decomposition. Three fractions were collected during the decomposition: (1) 2.5 g., b.p. 60–87°, n^{23}D 1.5768; (2) 1.0 g., b.p. 88–130°, n^{23}D 1.5779; (3) 2.5 g., b.p. 130–155°, n^{23}D 1.5874.

A one-gram sample of each fraction was oxidized in hot glacial acetic acid with excess hydrogen peroxide. Fraction 1 yielded 0.5 g. of sulfone, m.p. 110–126°; fraction 2 yielded 0.5 g. of sulfone, m.p. 115–122°; fraction 3 yielded 0.6 g. of sulfone, m.p. 113–122°. Each sample of sulfone was recrystallized three times from ethanol. The melting points remained essentially unchanged and mixed melting points of the three samples showed no depression.

Anal. Calcd. for $C_{16}H_{12}O_4NS$: C, 60.17; H, 5.46. Found: C, 60.18; H, 5.37.

Attempted Preparation of 1-Butylthio-2-nitroisobutane.—A 40% solution of formaldehyde (26.2 g., 0.35 mole of formaldehyde) was added to a solution of 2-nitropropane (31.2 g., 0.35 mole), butyl mercaptan (27.0 g., 0.30 mole) and piperidine (3 ml.). An exothermic reaction occurred. The mixture was heated on a steam-cone for 24 hours. The solution smelled strongly of mercaptan. Glacial acetic acid (0.5 ml.) was added and the reaction mixture heated for an additional 24 hours. The odor of mercaptan was still present. The solution was cooled and dissolved in 100 ml. of ether. The ethereal solution was washed with 50 ml. of 5% hydrochloric acid and then with water. The ethereal solution was dried and then distilled. All material boiling below 120° (b.p. of 2-nitropropane) was discarded. The residue boiled at 62–75° (3 mm.) and readily solidified. The solid was washed with a small amount of petroleum ether. There was obtained 16.4 g. of white solid melting at 80–83°. Recrystallization of the solid from carbon tetrachloride raised the melting point to 89.5–90.5°.

Anal. Calcd. for $C_4H_9O_3N$: C, 40.32; H, 7.61. Found: C, 40.03; H, 7.63.

The melting point of 2-nitro-2-methylpropanol (IV) is reported to be 82°.[6] Its *p*-toluenesulfonyl ester, prepared according to the procedure of Riebsomer,[7] melted at 73–74°. The reported melting point for the *p*-toluenesulfonate of 2-nitro-2-methylpropanol is 73–74°.

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[6] L. Henry, *Bull. soc. chim.*, [3] **13**, 1002 (1895).

[7] J. L. Riebsomer, *J. Org. Chem.*, **11**, 182 (1946).

MINNEAPOLIS 14, MINN.

RECEIVED OCTOBER 2, 1950

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ARKANSAS]

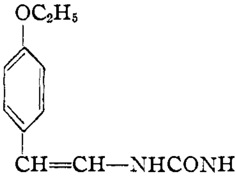
Vinylogy in Sweetening Agents. I. A Vinylog of Dulcin[1]

BY WILLIAM K. NOYCE, CHARLES H. COLEMAN AND JOHN T. BARR

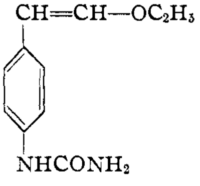
In order to study the principle of vinylogy in connection with the effects of functional groups on a physiological property such as taste, a vinylog of dulcin has been prepared. This involved the synthesis of several new compounds. The final product, *p*-ethoxystyrylurea, and two of the four intermediates have been isolated. This vinylog of dulcin was found to be sweet, but an intermediate, *p*-ethoxy-β-nitrostyrene, was not sweet although it is the vinylog of a sweet compound.

Although a great many individual facts are known and a considerable number of empirical rules have been formulated,[2] no basic underlying principle is known which relates the structure of an organic compound to its taste. For example, in the case of the sweetening agent, dulcin (*p*-ethoxyphenylurea), the substitution of a methoxy group for the ethoxy group does not destroy the sweetness,[3] nor does the substitution of a methyl group on the α-nitrogen of the urea.[4] However, neither the meta nor the ortho isomer of dulcin is sweet, nor is the resulting compound sweet when a methylene group is interposed between the phenyl group and the urea residue.[5] The purpose of this investigation is to study the functional relationship between groups in connection with the principle of vinylogy.[6] Since δ-ethoxybutylurea is not sweet,[7] it appears that more than merely the number of connecting carbon atoms is involved.

Assuming that the ethoxy group and the urea group are the functions whose relationships are involved, then the two simplest "vinylogs" of dulcin are *p*-ethoxystyrylurea (I) and *p*-ureidostyryl ethyl ether (II).



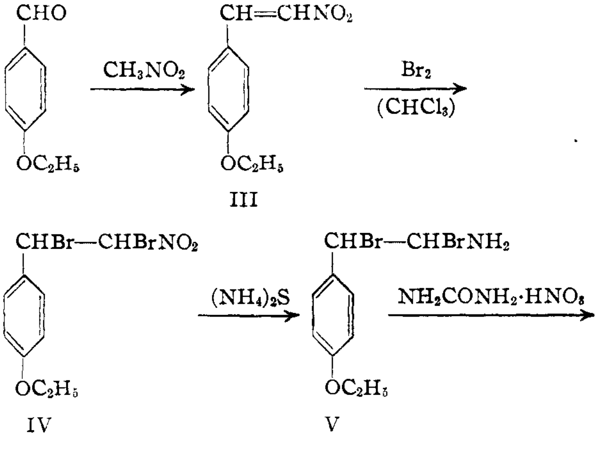
I



II

The vinylogs of the ortho isomer of dulcin are also of interest because of their structural similarities to dulcin itself.

Progress has been made toward the preparation of *o*-ethoxystyrylurea and *p*-ethoxystyrylurea has been synthesized by means of the steps



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[1] Presented before the Division of Organic Chemistry at the 118th Meeting of the American Chemical Society, Chicago, September 6, 1950.

[2] Moncrieff, "The Chemical Senses," John Wiley and Sons, Inc., New York, N. Y., p. 274 (1944).

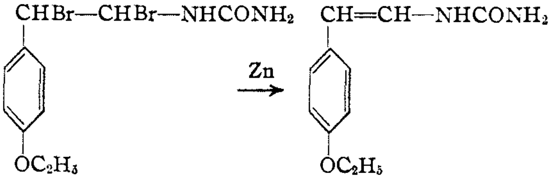
[3] Lorang, *Rec. trav. chim.*, **47**, 179 (1928).

[4] Bergmann, Camacho and Dreyer, *Ber. deut. pharm. Ges.*, **32**, 249 (1922).

[5] Wertheim, THIS JOURNAL, **57**, 545 (1935).

[6] Fuson, *Chem. Revs.*, **16**, 1 (1935).

[7] Wertheim, THIS JOURNAL, **56**, 735 (1934).



VI I

Experimental

Using *p*-hydroxybenzaldehyde from the Dow Chemical Company, *p*-ethoxybenzaldehyde was prepared in the usual manner by treatment with alkali and subsequent reaction with ethyl iodide. The succeeding compounds in the series were then prepared as indicated below.

***p*-Ethoxy-β-nitrostyrene (III)**.—With certain variations this compound was prepared by the method used by Rosenmund[8] for similar compounds. After dissolving 49.5 g. (0.33 mole) of *p*-ethoxybenzaldehyde and 21 g. (0.34 mole) of nitromethane in 70 ml. of ethanol, the mixture was cooled to 0°. This mixture was kept in an ice-bath and stirred constantly while a cold solution of 20 g. of potassium hydroxide in 20 ml. of water and 60 ml. of ethanol was added. It was added slowly and at such a rate that the temperature did not rise above 5°. When the reaction was complete, the mixture was diluted with 300 ml. of ice-water. The solution was then poured into a mixture of 40 ml. of concd. hydrochloric acid in one liter of water and ice. The product appeared as a yellow precipitate. This was filtered at once by suction and washed with cold water. Clusters of long, yellow needles formed when it was recrystallized from hot alcohol; yield 70%, m.p. 114–115°.

Since *p*-nitrophenetole is sweet,[2] it was thought that this vinylog might also be sweet, but it was practically tasteless.

Anal. Calcd. for $C_{10}H_{11}NO_3$: C, 62.16; H, 5.75; N, 7.36. Found: C, 61.90; H, 5.70; N, 7.25.

***p*-Ethoxy-β-nitrostyrene Dibromide (IV)**.—A solution of 10 g. (0.05 mole) of *p*-ethoxy-β-nitrostyrene in 60 ml. of chloroform was placed approximately 5 cm. from a clear, 150-watt light bulb. Then with constant shaking 8.3 g. (0.052 mole) of bromine was added in small portions. The addition reaction took place readily and the temperature rose about 10°. When all the bromine had been added and the reaction mixture had been allowed to stand for 15 minutes, it was a clear, light red color. After the chloroform had been evaporated by a stream of air, a yellow crystalline mass remained. This was recrystallized from 200 ml. of "isoöctane." After two recrystallizations the crystals were practically white, with a very faint yellow tinge. The compound showed no unsaturation when tested with permanganate. The yield was 15.5 g. (82%), m.p. 84.0 84.5°.

Anal. Calcd. for $C_{10}H_{11}Br_2NO_3$: C, 34.02; H, 3.14. Found: C, 34.69; H, 3.22.

***p*-Ethoxy-β-aminostyrene Dibromide (V)**.—The reduction of the nitro compound was first carried out by dissolving it in alcohol, making the solution basic with ammonium hydroxide and then passing in hydrogen sulfide. It was found, however, that better results were obtained by using ammonium sulfide. A solution of 28 g. (0.08 mole) of *p*-ethoxy-β-nitrostyrene dibromide in 200 ml. of ethanol was placed in a bath of cold water so that the temperature of the reaction mixture could be kept below 20°. Three equivalents (0.24 mole) of ammonium sulfide solution were added in small portions and with constant stirring. Heat was evolved, the mixture darkened somewhat and a precipitate of sulfur appeared. The mixture was stirred for 30 minutes after all of the sulfide had been added. It was then extracted with three 75-ml. portions of ether, and the ether allowed to evaporate until only a sirupy gum remained. Since this type of compound would be expected to be unstable, the crude product was used immediately in the next step without purification.

***p*-Ethoxy-β-ureidostyrene Dibromide (VI)**.—Eight grams (0.022 mole) of the crude *p*-ethoxy-β-aminostyrene dibromide was dissolved in 200 ml. of hot ethanol and 4 g. (0.032 mole) of urea nitrate was added to the solution. After refluxing for 7 hours, the mixture was diluted to 1000 ml. with cold water. The product was extracted from the resulting milky orange-yellow suspension with three portions of ether. The combined extracts were evaporated to a volume of 100 ml. and used directly in the subsequent preparation. The solution of the compound gave no indication of being sweet.

***p*-Ethoxystyrylurea (I)**.—Fifty ml. of the ether solution of *p*-ethoxy-β-ureidostyrene dibromide was refluxed for 5 hours with 10 g. of zinc powder. The mixture was allowed to stand overnight, then filtered and the ether solution evaporated over the steam-bath. The residue was a yellow-green oil which had a pleasant odor and a rather pleasant, quite sweet taste with a somewhat bitter after-taste. Unsaturation in the compound was indicated by the immediate decolorizing of bromine in carbon tetrachloride and an immediate reaction with dilute alkaline permanganate solution. After these tests were made, the oil was dissolved in 20 ml. of hot ethanol. The gray-green precipitate, which formed when the solution was chilled, was separated by suction filtration. It had practically no taste nor odor. The taste remained in the yellow-tan alcohol solution. (Since it was thought that this might be some of the unreacted bromine compound, it was refluxed in alcohol solution with additional zinc for 7 hours. Practically no additional product was formed.)

Several unsuccessful attempts to isolate the compound from the alcohol solution were made. Because of its high solubility in alcohol, even chilling the concentrated solution to −25° produced no crystals. The product was finally isolated by the following procedure. The oil (formed from the reaction with zinc) was steam distilled. The first part of the distillate was a milky-white suspension and a clear, light-yellow oil. The oil was extracted with ether and the ether evaporated. The resulting oil was dried over calcium chloride and then distilled at atmospheric pressure (732 mm.). Most of the product distilled below 230°. (The higher fractions did not respond readily to unsaturation tests and were not sweet.) On chilling the first fraction a few crystals were formed. These were removed by filtration and the sweet, yellow oil remaining was allowed to stand for several days in a desiccator over calcium chloride. Pale yellow needles (up to 5 mm. in length) gradually formed, m.p. 129.0–129.4°.

Anal. Calcd. for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.59. Found: C, 64.24; H, 6.90; N, 13.79.

The compound was sweet. Some of the tests were made with the pure crystals and others with the compound in solution. Water solutions were not very satisfactory due to the extreme insolubility of the compound. A mixture of water and alcohol was also used as a solvent. No "quantitative" tests for relative sweetness were made.

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RECEIVED OCTOBER 4, 1950

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(8) Rosenmund, *Ber.*, **42**, 4779 (1909).