Skraup[2] found difficulty in analyzing esters of mucic acid, which may be ascribed not only to the difficulty of complete combustion of esters in general but in this particular case to the formation of pyromucates which we have found difficult to burn completely. In spite of all precautions the analyses for carbon came out uniformly low, especially in the higher esters. The hydrogen determinations were satisfactory. Checks were made for each analysis.

In Table I are given the physical constants and results of analysis of the esters prepared.

Summary

The furoic acid esters of five normal and three secondary alcohols have been prepared and their properties reported.

New York, N. Y.

[Contribution from the Chemical Laboratory, Case School of Applied Science]

SOME PARA-PHENOXY-UREAS AND THIO-UREAS DERIVED FROM PARA-PHENOXY-ANILINE. THE EFFECT OF THE PHENOXY GROUP ON THE TASTE

By N. A. Lange and W. Robert Reed

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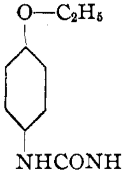
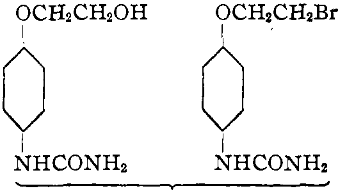
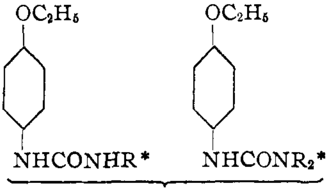
The taste of a compound is without a doubt related to its structure, since very slight changes to the molecule of a sweet substance often cause a complete loss of the property of sweetness. In the case of dulcin (*p*-ethoxyphenyl-urea), nearly every change in structure causes a lowering or complete loss in this repect. This can be seen in the following dulcin-like compounds[1]



Dulcin; sweet



Slightly sweet



Not sweet

*R = methyl, ethyl or phenyl

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[2] Skraup, *Monatsh.*, **14**, 476 (1893).

[1] Boedecker and Rosenbusch, *Ber. pharm. Ges.*, **30**, 251 (1920). Speckan, *ibid.*, **32**, 83 (1922). Thoms, *Z. angew. Chem.*, **37**, 809 (1924).

Although many relations between the color and the structure of compounds are known, in most cases the ability to predict a physiological action of an organic compound from its constitutional formula is quite obscure. The purpose of this investigation was to determine the effect on the taste of dulcin when the ethoxy group is replaced by the phenoxy group and to prepare other similar *p*-phenoxy substituted ureas. As is known, the introduction of a phenyl group into the molecule of a sweet tasting compound or the replacement of an alkyl group by a phenyl group causes a diminution of the sweetness or the production of a bitter taste.[2] In the case of the sweet compounds α-alanine, glycine and glycol, the introduction of a phenyl group to form α-phenylalanine, causes only a lowering in sweetness, whereas phenylglycine is tasteless and phenylglycol is bitter. It has been found that this same rule applies to the compounds which we have prepared, as all of them were found to lack a sweet taste. Because of their insolubility in water, the tests were made with solutions in alcohol diluted with water. In the case of *p*-phenoxy-thiocarbanilide and of *p*-phenoxyphenyl-thio-urea, a slightly bitter taste was found to be present and this no doubt is caused by the replacement of sulfur for oxygen. This effect of sulfur in the thion group also fits the general rule that such compounds are bitter. But it is also to be noted that the phenoxy group in these cases causes a lowering of the bitter taste. The exceedingly bitter taste of *s*-diphenyl-thio-urea (thiocarbanilide) was pointed out by Hofmann,[3] and likewise the same property of bitterness of *o*- and *p*-ethoxyphenyl-thio-urea has been recorded by Berlinerblau.[4] The effect of sulfur in changing the taste from sweet to bitter is strikingly shown by dulcin and its thio-urea analog.

Phenyl ether, which is obtained as a by-product in the preparation of phenol from the interaction of chlorobenzene with sodium hydroxide, formed the starting point of the syntheses. On nitration *p*-nitrophenyl ether was obtained, which was reduced to the amino derivative and the latter converted into the thio-urea or urea by treatment with a thiocyanate or cyanate. In this way the following compounds were prepared: *p*-phenoxyphenyl-urea, *p*-phenoxy-carbanilide, *p*-phenoxy-*p*′-methyl-carbanilide, α-*p*-phenoxyphenyl-β-α-naphthyl-urea, *p*-phenoxyphenyl-thiourea, *p*-phenoxy-thiocarbanilide and *p*,*p*′-diphenoxy-thiocarbanilide.

Experimental Part

Nitration of Phenyl Ether. Preparation of *p*-Nitrophenyl Ether.—*p*-Nitrophenyl ether was first prepared by Haeussermann and Teichmann[5]

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[2] Sternberg, *Arch. Anat. Physiol.*, **1899**, p. 367.

[3] Hofmann, *Ann.*, **70**, 147 (1849).

[4] Berlinerblau, *J. prakt. Chem.*, [2] **30**, 108 (1884).

[5] Haeussermann and Teichmann, *Ber.*, **29**, 1446 (1896).

through the interaction of potassium phenolate and *p*-chloronitrophenol and found to melt at 61°; a similar method using *p*-bromonitrophenol was employed by Jones and Cook;[6] their product, however, melted at 123°. Mailhe and Murat were the first to carry out the direct nitration of phenyl ether and obtained a mononitro derivative melting at 56°. The papers of Mailhe and Murat[7] and Mailhe and Moreau[8] were lacking in details on the direct nitration, the first paper stating that nitration was accomplished with fuming nitric acid at 50°. In addition to being misleading as to the temperature, their record gives no hint as to the concentrations used. In the later paper a suggestion of raising the temperature until red fumes are evolved is vague and, again, no concentrations are given. However, the method devised in this investigation closely parallels that of the last paper. Nitric acid, d. 1.4, has practically no action on solutions of phenyl ether in glacial acetic acid except in very concentrated solutions. Almost any concentration of fuming nitric acid (d., 1.5) at 50° gave a brown or green reaction product from which white crystals, melting at 95–97° (uncorr.), were sometimes obtained; this is probably the tetranitro derivative described by Mailhe and Murat. After many trials under various conditions the following procedure was adopted.

Fifty g. of phenyl ether is dissolved in 120 cc. of glacial acetic acid and the solution heated to boiling under a reflux condenser. To the gently boiling solution a mixture of 50 cc. of nitric acid (d., 1.5) and 50 cc. of glacial acetic acid is added from a dropping funnel during the course of about three hours. If the addition is too rapid, especially at first, the reaction soon becomes vigorous and beyond easy control. After all of the acid has been added, the heating is continued for about one hour. The reaction product is poured into 4 to 5 liters of cold water and washed several times with fresh water. The oil is dried on a steam-plate and cooled. Crystals of *p*-nitrophenyl ether are obtained by dissolving this oil in alcohol at a temperature slightly above room temperature and cooling slowly to the temperature of an ice-salt mixture. If an attempt is made to get crystals from a solution more concentrated than is obtained near room temperature or by cooling too rapidly, an oil separates. The crystalline product so obtained can now be purified by recrystallizing from a warmer and more concentrated alcoholic solution. By this method a yield of 19 g. of crude crystals was obtained. Three of the oily residues from which the *p*-nitrophenyl ether had been extracted were distilled under reduced pressure. Under a pressure of 3 cm. of mercury a fraction up to 225° resulted that contained 15 g. of phenyl ether; most of the remainder distilled between 225° and 232° and from this a solid separated which when crystallized from alcohol melted at 141–143° and was probably the *p,p'*-dinitro derivative for which Mailhe reports a melting point of 138–139°. An attempt to separate the mono-*p*-nitro derivative by distillation under 3 cm. pressure gave a good product at the expense of the yield. It distilled between 225° and 230° giving about 10 g. of product. Steam distillation can be employed, after removal of the acetic acid by distillation, to separate the phenyl ether from the nitro compounds but it is a long process for a doubtful gain in yield. With a recovery of 5 g. of phenyl ether, the 19 g. represents a 33% yield of the nitro

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[6] Jones and Cook, THIS JOURNAL, **38,** 1534 (1916).

[7] Mailhe and Murat, *Compt. rend.*, **154,** 716 (1912).

[8] Mailhe and Moreau, *ibid.*, **154,** 1240 (1912).

derivative. *p*-Nitrophenyl ether is insoluble in water, very soluble in ether or carbon tetrachloride and fairly soluble in alcohol; m. p., 56–57° (corr.).

Preparation of *p*-Phenoxy-anilide (*p*-Aminophenyl Ether).—*p*-Phenoxy-aniline was prepared in almost calculated yield by treating equal weights of nitrophenyl ether and tin with sufficient hydrochloric acid (d., 1.2) to equal 3 cc. for each gram of tin. The mixture is heated to boiling to start the reaction. After all of the oil has dissolved, the solution is diluted with water, made alkaline with sodium hydroxide, steam distilled and the oil separated from the distillate. In place of steam distilling the reaction mixture, the amine can be isolated also by extracting the alkaline solution with ether and then saturating the ether extract with hydrogen chloride. The amine hydrochloride which separates as a crystalline mass is filtered off and converted to the free base by treatment with alkali in aqueous solution. The free base after being boiled with charcoal in alcoholic solution and this solution diluted with water, forms colorless crystals which melt at 82° (corr.) and the liquid substance boils at about 315–320° (3 cm.). The free base is converted to the hydrochloride by being melted and poured during stirring into hot hydrochloric acid. The solution is treated with charcoal and filtered; on cooling, fine, white needles separate. It melts at 222° (corr.), is partially hydrolyzed in an aqueous solution and gradually turns brown on exposure to the air.

Preparation of *p*-Phenoxyphenyl-urea, $C_6H_5.O.C_6H_4.NH.CO.NH_2$.—To 5 g. of *p*-phenoxy-aniline hydrochloride suspended in about 75 cc. of cold water, 2.5 g. of potassium cyanate is added. A white precipitate is formed and after the mixture has been occasionally stirred for an hour, the product is filtered off. The solid is extracted with hot alcohol, filtered off and warm water is added to the solution, care being taken not to add sufficient to give a permanent precipitate. On cooling, white crystals of the urea separate; an 86% yield was obtained. After recrystallizing from alcohol it melts at 178° (corr.). *p*-Phenoxyphenyl-urea is soluble in alcohol, ether, acetone or glacial acetic acid, fairly soluble in chloroform, and insoluble in petroleum ether, carbon tetrachloride or water. The compound was found to be tasteless.

Anal. Calcd. for $C_{13}H_{12}O_2N_2$: C, 68.39; H, 5.30; N, 12.3. Found: C, 68.59; H, 5.32; N, 12.1.

Preparation of *p*-Phenoxy-carbanilide (α-*p*-Phenoxyphenyl-β-phenyl-urea), $C_6H_5.O.C_6H_4.NH.CO.NH.C_6H_5$.—Equimolecular quantities of *p*-phenoxy-aniline and phenylisocyanate are stirred together in a beaker. The reaction mixture becomes warm and soon solidifies. A 70% yield of colorless crystals of *p*-phenoxy-carbanilide is obtained by recrystallizing from alcohol and decolorizing with charcoal. The compound is fairly soluble in alcohol, acetone, acetic acid or chloroform, very slightly soluble in benzene or carbon tetrachloride and insoluble in petroleum ether or water; m. p., 201° (corr.). Solutions of the compound in alcohol diluted with water are tasteless.

Anal. Calcd. for $C_{19}H_{16}O_2N_2$: C, 74.96; H, 5.30; N, 9.2. Found: C, 75.10; H, 5.32; N, 9.3.

Preparation of *p*-Phenoxy-*p*'-methyl-carbanilide (α-*p*-phenoxyphenyl-β-*p*-tolylurea), $C_6H_5.O.C_6H_4.NH.CO.NH.C_6H_4.CH_3$.—Equimolecular quantities of *p*-phenoxyaniline and *p*-tolylisocyanate are stirred together in a beaker. Heat is evolved and the mixture soon solidifies giving a 90% yield of the urea. Colorless crystals of *p*-phenoxy-*p*'-methyl-carbanilide are obtained by recrystallizing from ethyl alcohol. The compound is fairly soluble in alcohol, acetone or acetic acid, slightly soluble in benzene, very slightly soluble in ether, chloroform or carbon tetrachloride and insoluble in petroleum ether or water; m. p., 204° (corr.). Solutions of the compound in alcohol diluted with water are tasteless.

Anal. Calcd. for $C_{20}H_{18}O_2N_2$: C, 75.43; H, 5.70. Found: C, 75.54; H, 5.83.

Preparation of α-*p*-Phenoxyphenyl-β-α-naphthyl-urea, $C_6H_5.O.C_6H_4.NH.CO.NH.C_{10}H_7$.—This compound was obtained by mixing equimolecular quantities of *p*-phenoxyaniline and α-naphthylisocyanate. Heat is evolved and, on cooling, the mixture solidifies with the formation of an 86% yield of the urea. Crystallization from hot acetone with the addition of warm water gives colorless crystals; m. p., 216° (corr.). The compound is fairly soluble in acetic acid or acetone, slightly soluble in alcohol or benzene, very slightly soluble in chloroform or carbon tetrachloride and insoluble in petroleum ether or water. Solutions of the compound in alcohol diluted with water are tasteless.

Anal. Calcd. for $C_{23}H_{18}O_2N_2$: C, 77.93; H, 5.12. Found: C, 78.15; H, 5.12.

Preparation of *p*-Phenoxyphenyl-thio-urea, $C_6H_5.O.C_6H_4.NH.CS.NH_2$.—A suspension of 3.25 g. of *p*-phenoxy-aniline hydrochloride in 10 cc. of cold water is treated with 3 g. of potassium thiocyanate dissolved in cold water. The mixture is evaporated to dryness on a steam-bath, the residue treated with water, filtered and the insoluble portion dried. On crystallization from alcohol an 84% yield of *p*-phenoxyphenyl-thiourea was obtained as colorless crystals which are fairly soluble in alcohol, acetone, chloroform or acetic acid, slightly soluble in benzene, very slightly soluble in ether or carbon tetrachloride and insoluble in petroleum ether or water; m. p., 184° (corr.). Solutions of the compound in alcohol diluted with water have a very slightly bitter taste. In preparing this compound, when the reaction is carried out in a larger volume of water (75–100 cc.) the amine hydrochloride dissolves after the potassium thiocyanate is added and after some time crystals begin to separate from the solution. This product softens at about 136°, solidifies again and finally melts at 180–184°. When free alkalies are added to solutions of the compound melting at 136°, the free base of *p*-phenoxy-aniline is obtained. The compound is probably the thiocyanate salt of the amine which rearranges to the thio-urea when heated to its melting point.

Anal. Calcd. for $C_{13}H_{12}ON_2S$: C, 63.89; H, 4.95; N, 11.5; S, 13.1. Found: C, 64.18; H, 5.05; N, 11.3; S, 13.5.

Preparation of *p*-Phenoxy-thiocarbanilide (**α-*p*-Phenoxyphenyl-β-phenyl-thiourea**), $C_6H_5.O.C_6H_4.NH.CS.NH.C_6H_5$.—Equimolecular quantities of *p*-phenoxy-aniline and phenylisothiocyanate are mixed; the solution becomes warm and solidifies. The compound, obtained in 90% yield, on treatment with charcoal and recrystallization from alcohol gave colorless crystals; m. p., 140° (corr.); it is very soluble in acetone, fairly soluble in alcohol, acetic acid or chloroform, very slightly soluble in ether or carbon tetrachloride and insoluble in petroleum ether or water. Solutions of the compound in alcohol diluted with water have a very slightly bitter taste.

Anal. Calcd. for $C_{19}H_{16}ON_2S$: C, 71.20; H, 5.04; N, 8.8; S, 10.0. Found: C, 71.53; H, 4.97; N, 8.9; S, 9.7.

Preparation of *p,p'*-Diphenoxy-thiocarbanilide (***s*-*p*-Phenoxyphenyl-thio-urea**), $(C_6H_5.O.C_6H_4.NH)_2.CS$.—Ten g. of *p*-phenoxy-aniline, 6.5 g. of carbon disulfide, 7 g. of ethyl alcohol and 0.5 g. of sodium hydroxide are boiled under a reflux condenser for one and a half hours. The excess of carbon disulfide and alcohol is removed by distillation and the residue poured into water. The solid which separates is filtered off, washed first with dil. hydrochloric acid, then with water and dried. When crystallized from alcohol it forms colorless crystals; m. p., 172° (corr.); yield, 36%. It is very soluble in acetone, fairly soluble in alcohol or chloroform, very slightly soluble in benzene, ether or carbon tetrachloride and insoluble in petroleum ether or water. Solutions of the compound in alcohol diluted with water are tasteless.

Anal. Calcd. for $C_{25}H_{20}O_2N_2S$: C, 72.77; H, 4.89; N, 6.8; S, 6.8. Found: C, 73.09; H, 4.98; N, 7.0; S, 6.8.

Summary

The preparation of *p*-nitro- and of *p*-amino-diphenyl ether has been described; from the amino compound seven differently substituted phenoxy-ureas and thio-ureas have been prepared. These ureas which are analogs of the sweet compound dulcin (*p*-phenetyl-urea) are without a sweet taste and in the case of two of the thio-ureas the taste was found to be bitter, although not as bitter as that of other very closely related thio-ureas, thus indicating the effect of the phenoxy group in decreasing both the sweet and the bitter taste.

CLEVELAND, OHIO

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

THE PREPARATION AND USE OF ALDEHYDE ESTERS FORMED BY OZONATION OF THE METHYL ESTERS OF VARIOUS UNSATURATED ACIDS

BY C. R. NOLLER[1] WITH ROGER ADAMS

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The aldehyde esters formed by ozonation of such esters as methyl oleate, methyl undecylenate and methyl erucate should have wide application in synthetic work and should offer valuable starting materials, especially for the synthesis of acids of high molecular weight. This research had as its object the study of the experimental details by which these aldehyde esters could be readily made. Satisfactory results were obtained and no difficulty was encountered in the isolation of over 55% of the calculated amount of aldehyde ester boiling over a range of 5°. With especial care these yields could be increased. In addition, pelargonic aldehyde in yields of 60–70% was obtained from methyl oleate and methyl erucate.

Previous investigators have ozonized oleic,[2] elaidic,[2a] linoleic,[3] α- and β-linolenic,[4] ricinoleic,[3] erucic,[5] brassidic,[5] undecylenic[3b] and eleostearic[6] acids and the corresponding aldehyde acids or their oxidation products were obtained. Of the esters of the unsaturated acids, triolein,[7] ricin-

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[1] This communication is an abstract of a portion of a thesis submitted by C. R. Noller in partial fulfilment of the requirements for the Degree of Doctor of Philosophy in Chemistry at the University of Illinois.

[2] (a) Harries and Thieme, *Ann.*, **343**, 354 (1905); *Ber.*, **39**, 2844 (1906). (b) Molinari and Soncini, *Ber.*, **39**, 2735 (1906). (c) Harries, *Ber.*, **39**, 3728 (1906). (d) Harries and Turk, *Ber.*, **39**, 3732 (1906). (e) Molinari and Barosi, *Ber.*, **41**, 2794 (1908). (f) Harries and Franck, *Ann.*, **374**, 356 (1910). (g) See also Brit. pat. 11,165, **1901**.

[3] (a) Thieme, *Inaug. Diss.*, Kiel, **1906**. (b) Noorduyn, *Rec. trav. chim.*, **38**, 317 (1919).

[4] Erdmann, Bedford and Raspe, *Ber.*, **42**, 1334 (1909).

[5] Ref. 3 a. Holde and Zadek, *Ber.*, **56**, 2052 (1923).

[6] Majima, *Ber.*, **42**, 674 (1909).

[7] Molinari and Fenaroli, *Ber.*, **41**, 2789 (1908).