[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF CORNELL UNIVERSITY]

# THE STRUCTURE OF PHENOLPHTHALEIN OXIME

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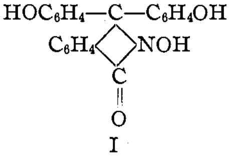
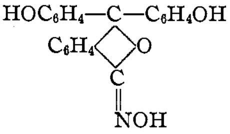
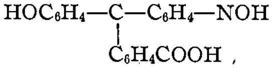
Two formulas (I and II) have been proposed for phenolphthalein oxime[1] since it has been shown that Formula III proposed by Friedländer



I



II

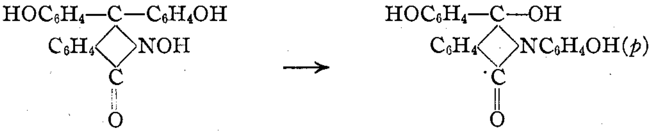


$$HOC_6H_4-\underset{\substack{| \\ C_6H_4COOH}}{C}-C_6H_4-NOH\ ,$$

III

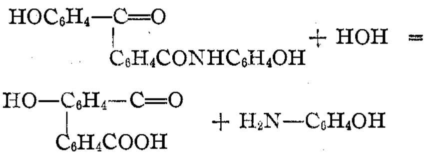
is incorrect.

In order to explain the quantitative decomposition of the oxime by dil. sulfuric acid into *p*-hydroxybenzoyl-*o*-benzoic acid and *p*-aminophenol, Orndorff and Murray assume Formula I for the compound. They further assume that phenolphthalein oxime, like the oximes of the ketones, undergoes the Beckmann rearrangement giving an intermediate product which is the *p*-hydroxyanilide of *p*-hydroxybenzoyl-*o*-benzoic acid.



Phenolphthalein oxime Intermediate product

This intermediate product or its ketone form then hydrolyzes into *p*-hydroxybenzoyl-*o*-benzoic acid and *p*-aminophenol.



$$HOC_6H_4-\underset{\substack{| \\ C_6H_4CONHC_6H_4OH}}{C{=}O} + HOH =$$

$$HO-C_6H_4-\underset{\substack{| \\ C_6H_4COOH}}{C{=}O} + H_2N-C_6H_4OH$$

The fact that *p*-hydroxyphthalanil is obtained when an excess of hydroxylamine is used in the preparation of the oxime or as H. Meyer[2] found by heating the oxime with a solution of hydroxylamine hydrochloride is also

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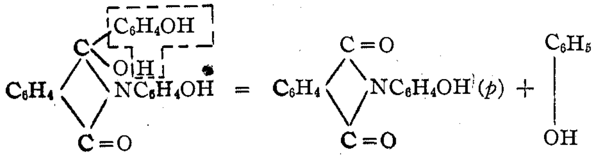
[1] See R. Meyer and Kissen, *Ber.*, **42**, 2825 (1909), and Orndorff and Murray, THIS JOURNAL, **39**, 689 (1917).

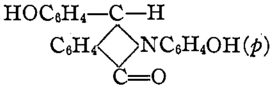
[2] Meyer, *Monatsh.*, **20**, 346 (1899).

explained by assuming the formation of the intermediate product which then breaks down into *p*-hydroxyphthalanil and phenol.



Intermediate product *p*-Hydroxyphthalanil Phenol

The reduction product of phenolphthalein oxime which H. Meyer and R. Meyer have shown to have the structure



is also formed according to Orndorff and Murray not from the oxime but from the intermediate product.

It will be seen from the foregoing that it would be highly desirable to prove that phenolphthalein oxime undergoes the Beckmann rearrangement like the ketoximes, to isolate the intermediate product and show that it undergoes the above changes. The present paper shows how this was accomplished.

## Experimental Part

R. Meyer and Kissen[1] have prepared what they call a triacetate of the oxime by heating it with acetic anhydride and sodium acetate. As this substance is *colorless*, whereas the oxime is *yellow*, it was thought that it might be the triacetate of the intermediate product and that when the oxime is acetylated it undergoes the Beckmann rearrangement. If this is true then it seemed quite likely that on saponification the triacetate would give the intermediate product and not the oxime. Experiment showed that this idea was correct.

**Triacetate of the *p*-Hydroxyanilide of *p*-Hydroxybenzoyl-*o*-benzoic Acid.**—This was made from the oxime by the method given by R. Meyer and Kissen[1] and carefully purified by recrystallization from acetone. It crystallized in *colorless* needles that melted at 235°. R. Meyer and Kissen give the melting point of their product as 229–230°. Analyses on the product dried in a vacuum desiccator over concd. sulfuric acid gave the following results:

*Analyses.* Subs., 0.2388, 0.2238: $CO_2$, 0.5939, 0.5568; $H_2O$, 0.1010, 0.0940. Calc. for $C_{26}H_{21}O_7N$: C, 67.95; H, 4.61. Found: C, 67.82, 67.85; H, 4.73, 4.70.

Subs., 1.0267, 1.0500: cc. of 0.1 *N* $H_2SO_4$, 23.14, 23.53. Calc. for $C_{26}H_{21}O_7N$: N, 3.05. Found: 3.16, 3.14.

Subs., 0.5004: 32.62 cc. of 0.1 *N* NaOH. Calc. for $C_{20}H_{12}O_4N(COCH_3)_3$: $CH_3CO$, 28.11. Found: 28.10.

In view of the statement of H. Meyer[3] that there are at least 3 triacetates of the oxime, all insoluble in alkali and that he had already obtained 2 of them in pure form and

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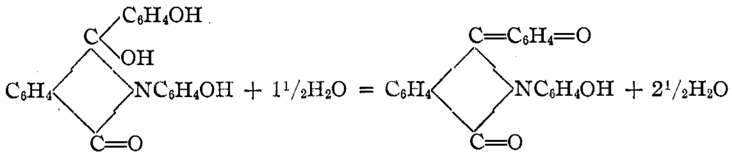
[3] H. Meyer, *Monatsh.*, **17**, 440 (1896).

had analyzed them, the crude acetate was subjected to careful fractional crystallization. Only the triacetate melting at 235° was obtained.

**Saponification of the Triacetate by Sulfuric Acid. The Intermediate Product.**—The triacetate is saponified in the cold by conc. sulfuric acid. A dark red, viscous solution was formed. This was gradually poured into crushed ice, the solution was vigorously stirred and finally diluted with a great amount of water, filtered and allowed to stand. A yellow crystalline powder settled. This was freed from sulfuric acid by dissolving it in a cold 4% solution of sodium hydroxide and reprecipitating it with a slight excess of very dilute hydrochloric acid. The colorless precipitate after being washed with water was boiled with water. It first melted, then solidified and finally all passed into solution on boiling with sufficient water. As the solution cooled, small colorless, flaky crystals formed that melted at 135° with decomposition. The substance loses very little weight in a vacuum desiccator. The substance dried in a desiccator gave the following results on analysis.

*Analyses.* Subs., 0.2908, 0.2995, 0.2961: $CO_2$, 0.7110, 0.7324, 0.7246. $H_2O$, 0.1334, 0.1366, 0.1358. Subs., 1.0010, 1.0007: cc. of 0.1 *N* $H_2SO_4$, 28.2, 28.0. Calc. for $C_{20}H_{12}ON(OH)_3 + 1^1/_2H_2O$: C, 66.65; H, 5.04; N, 3.89. Found: C, 66.68, 66.69, 66.74; H, 5.13, 5.10, 5.13; N, 3.92, 3.92.

The above results show that the substance is the *p*-hydroxyanilide of *p*-hydroxybenzoyl-*o*-benzoic acid with 1.5 molecules of water of crystallization. An attempt was made to determine the water of crystallization by heating the substance in an atmosphere of carbon dioxide at 95°. Water vapor was given off and the substance melted to a dark red liquid which solidified on cooling to a dark red glass; 0.4892 g. of substance lost 0.0639 g. of water after 6 hours' heating; the calculated loss for 2.5 molecules of water is 0.0640 g. Thus, the intermediate product when heated not only loses all its water of crystallization but also an additional molecule of water of constitution as shown in the following equation.



An attempt made to convert the red glass into the intermediate product by boiling it with water was unsuccessful. The red compound is very difficultly soluble in hot water and only after prolonged boiling with water imparts a faint pink color to it. It is very soluble in dilute solutions of alkalies, giving a dark green solution. When this alkaline solution is acidified a yellow amorphous precipitate is formed. An attempt was also made to get the intermediate product in the anhydrous form by recrystallizing it from boiling water. The product, however, had the same melting point and on heating lost the same amount of water (*i. e.*, 2.5 molecular equivalents) as before.

The action of organic solvents on the intermediate product is very remarkable. Acetone, ethyl alcohol, methyl alcohol, or ethyl acetate dissolves it readily and the recrystallized product from each of these solvents has a different melting point. That from acetone melts at 94–95°, from methyl alcohol at 125°, from ethyl alcohol at 130° and from ethyl acetate at 195–198°. The intermediate product is slightly soluble in hot benzene or in hot toluene and insoluble in ether, ligroin, chloroform or carbon tetrachloride. The product crystallized from ethyl acetate seems to have the formula $C_{20}H_{12}ON(OH)_3 + {}^1/_2CH_3COOC_2H_5$ from the analysis.

*Analysis.* Subs., 0.6675: 19.11 cc. of 0.1 *N* $H_2SO_4$. Calc. for $C_{20}H_{12}ON(OH)_3 + {}^1/_2CH_3COOC_2H_5$: N, 3.92. Found: 4.01.

Subs., 0.3230. Calc. loss for $H_2O + {}^1/_2CH_3COOC_2H_5$: 0.0543 g. Loss after heating for 5 hours at 95°, 0.0540 g.

The odor of ethyl acetate was detected during the heating and a red glass was left in the boat.

**Saponification of the Triacetate by Alkali.**—Twenty g. of the triacetate, made from the oxime, was treated with 200 cc. of a 4% solution of sodium hydroxide. All of it dissolved in the cold after the solution stood a few hours and was shaken occasionally. The solution was colored yellow. If allowed to stand for a few days, it becomes green. The yellow solution was acidified with dil. hydrochloric acid and a white flocculent precipitate was obtained. This was collected on a filter, washed and boiled with a large amount of water. It acted exactly like the intermediate product obtained from the triacetate by saponification with conc. sulfuric acid. It first melted under the water, then solidified and finally all went into solution on boiling it with sufficient water. The crystals obtained from this solution on cooling were identical with those of the intermediate product made by saponification of the triacetate with concd. sulfuric acid and had the same m. p. The substance also gave the same reduction product, the same *p*-hydroxyphthalanil, the same dibenzoate, the same triacetate and the same trimethyl ether as the intermediate product made from the triacetate by saponification with concd. sulfuric acid. There is no doubt of the identity of the 2 products. This method of saponification of the triacetate gives a quantitative yield of the intermediate product and is better than the one with concd. sulfuric acid. The intermediate product made in this way also lost the same amount of water when heated and gave a red glass (0.4832 g. lost 0.0606 g. after 6 hours at 92°; calc. for $2^1/_2$ mols. of $H_2O$, 0.0603 g.).

**Hydrolysis of the Intermediate Product with Dilute Sulfuric Acid.**—On boiling the intermediate product with dil. sulfuric acid (1:8), it is hydrolyzed to *p*-hydroxybenzoyl-*o*-benzoic acid and *p*-aminophenol just as the oxime is. A quantitative determination resulted as follows: 1.0037 g. of substance gave 0.5759 g. of *p*-hydroxybenzoyl-*o*-benzoic acid and 0.2883 g. of *p*-aminophenol. The calculated amounts are *p*-hydroxybenzoyl-*o*-benzoic acid, 0.6187 g.; *p*-aminophenol, 0.3039 g.

**Decomposition of the Intermediate Product with Hydroxylamine Hydrochloride.**—Three g. of the intermediate product was heated with a concd. solution of hydroxylamine hydrochloride. After a short time, long colorless needles separated. These were recrystallized from dil. alcohol and found to melt at 288° with decomposition—as in the case of *p*-hydroxyphthalanil obtained from the oxime by the same treatment. A qualitative test for phenol, the other product of the decomposition, was also obtained. A Kjeldahl analysis of the product melting at 288° showed that it was *p*-hydroxyphthalanil.

*Analysis.* Subs., 0.3370: cc. of 0.1 *N* $H_2SO_4$, 14.14. Calc. for $C_{24}H_9O_3N$: N, 5.86. Found: 5.88.

**Reduction of the Intermediate Product.**—Five g. of the intermediate product was dissolved in about 60 cc. of dil. alcohol and 5 cc. of concd. sulfuric acid. Zinc dust was then added and the mixture carefully heated. The red color of the solution gradually faded to a light yellow. The zinc was then filtered off and the filtrate poured into water. The white precipitate obtained was recrystallized from dil. alcohol and found to melt at 256°—the same melting point as that of the reduction product made from the oxime by the same method. A mixture of the two products melted sharply at the same temperature. An acetyl derivative of the reduction product was also made, m. p., 205–208°, the melting point given by Herzig and H. Meyer for the diacetate of the reduction product.

**Acetylation of the Intermediate Product.**—Acetylation of the intermediate product with acetic anhydride and sodium acetate gave the same triacetate as was obtained from the oxime.

The product crystallized from acetone had the same melting point, and the same chemical and physical properties as the triacetate made from the oxime. Kjeldahl analyses on the substance dried in a desiccator also showed that it was identical with the triacetate made from the oxime.

*Analyses.* Subs., 0.9522, 0.9647: cc. of 0.1 *N* $H_2SO_4$, 20.86, 21.30. Calc. for $C_{26}H_{21}O_7N$: N, 3.05. Found: 3.07, 3.09.

**Benzoylation of the Intermediate Product.**—R. Meyer and Kissen[1] made what they call a tribenzoate of the oxime by benzoylating the oxime by the Schotten-Baumann reaction. It was thought that this benzoate might be the benzoate of the intermediate product, as in the case of the triacetate made from the oxime.

Ten g. of the intermediate product was dissolved in 150 cc. of 20% sodium hydroxide solution and an excess of benzoyl chloride was added, a little at a time while the mixture was shaken vigorously. A white precipitate was formed. It was washed with a dilute solution of sodium hydroxide, boiled with water to remove benzoic acid and then recrystallized from methyl alcohol. It melted at 227° and the melting point did not change when the substance was recrystallized from ethyl alcohol and from acetone. R. Meyer and Kissen give the melting point of their tribenzoate as 175°. Kjeldahl determinations of the substance dried in a desiccator gave the following results.

*Analyses.* Subs., 0.7828, 0.7815: cc. of 0.1 *N* $H_2SO_4$, 14.70, 15.09. Calc. for $C_{20}H_{13}O_4N(COC_6H_5)_2$: N, 2.59. Found: 2.63, 2.70.

This indicates that the substance is a dibenzoate instead of a tribenzoate. Further evidence of this was secured from the results of combustion analyses.

*Analyses.* Subs., 0.2994, 0.3095: $CO_2$, 0.8259, 0.8536; $H_2O$, 0.1158, 0.1228. Calc. for $C_{20}H_{13}O_4N(COC_6H_5)_2$: C, 75.39; H, 4.28. Found: C, 75.23, 75.21. H, 4.33, 4.44.

An attempt was made to obtain a mono-acetate of this dibenzoate by boiling it with acetic anhydride but the product was the triacetate of the intermediate product.

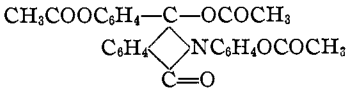
**Benzoylation of Phenolphthalein Oxime.**—Meyer and Kissen's experiment was repeated using exactly the same quantity of materials that they specify. The same dibenzoate was obtained as in benzoylating the intermediate product. It melted at 227° and gave the following results on analysis.

*Analyses.* Subs., 0.4112, 0.4042: cc. of 0.1 *N* $H_2SO_4$, 7.45, 7.64. Calc. for $C_{20}H_{13}O_4N(COC_6H_5)_2$: N, 2.59. Found: 2.54, 2.65.

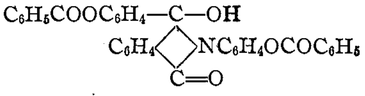
Subs., 0.3143: $CO_2$, 0.8679; $H_2O$, 0.1208. Calc. for $C_{20}H_{13}O_4N(COC_6H_5)_2$: C, 75.39; H, 4.28. Found: C, 75.31; H, 4.30.

Repeated attempts to make the tribenzoate described by Meyer and Kissen were unsuccessful.

It will be seen from these results that when the oxime is acetylated and benzoylated, it undergoes the Beckmann rearrangement and gives the triacetate and the dibenzoate of the intermediate product. These have the following structural formulas.



Triacetate



Dibenzoate

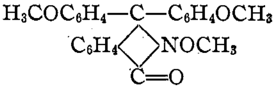
**Methylation of the Intermediate Product.**—R. Meyer and Spengler[4] have made the trimethyl ether of phenolphthalein oxime by methylating it in alkaline solution with dimethyl sulfate. As they describe this ether as almost colorless, it was thought that it might be the trimethyl ether of the intermediate product.

Five g. of the intermediate product was dissolved in 60 cc. of 30% of sodium hydroxide solution in a stoppered flask and an excess of dimethyl sulfate gradually added with vigorous shaking. The reaction soon took place with the evolution of heat and a white solid separated. This was collected, washed with water and recrystallized from methyl alcohol. The melting point of the recrystallized product was found to be 131–133°. Meyer and Spengler give the melting point of the trimethyl ether of the oxime as 145–146°. Phenolphthalein oxime was therefore methylated with dimethyl sulfate by the method given by Meyer and Spengler. The melting point of the ether recrystallized from both methyl alcohol and acetone was 145–146°; but the crystals are distinctly *yellow*, while those of the ether made from the intermediate product are *colorless*. Kjeldahl analyses were made on both substances and the results show that both are trimethyl ethers.

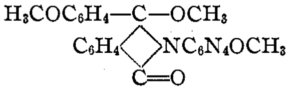
*Analyses.* (1) Trimethyl ether of the intermediate product. Subs., 0.5182, 0.5154: cc. of 0.1 *N* $H_2SO_4$, 13.33, 13.62. Calc. for $C_{20}H_{12}ON(OCH_3)_3$: N, 3.73. Found: 3.60, 3.70.

(2) Trimethyl ether of the oxime (yellow). Subs., 0.5150: cc. of 0.1 *N* $H_2SO_4$, 13.91. Calc. for $C_{20}H_{12}ON(OCH_3)_3$: N, 3.73. Found: 3.78.

It will be seen from these results that the 2 ethers are isomeric and that the oxime does not undergo the Beckmann rearrangement when methylated in alkaline solution with dimethyl sulfate. The structures of the two compounds are represented as follows.

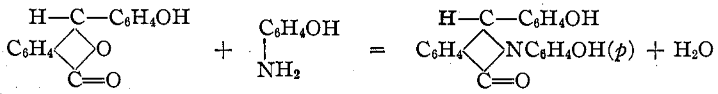


Trimethyl ether of the oxime



Trimethyl ether of the intermediate product

**Synthesis of the Intermediate Product.**—H. Meyer and R. Meyer have both made the reduction product of the oxime synthetically by heating *p*-hydroxy-phenylphthalide with *p*-aminophenol.



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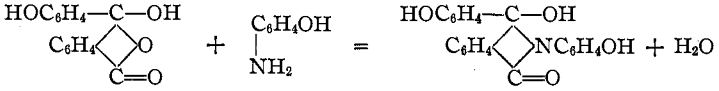
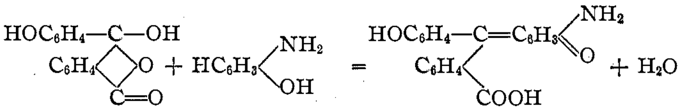
[4] R. Meyer and Spengler, *Ber.*, **36**, 2964 (1903).

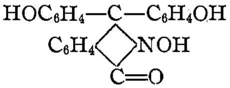
It was thought that *p*-hydroxybenzoyl-*o*-benzoic acid and *p*-aminophenol might react in a similar manner.



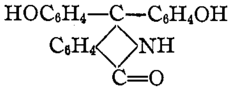
Eleven g. of *p*-hydroxybenzoyl-*o*-benzoic acid and 5 g. of *p*-aminophenol were melted together. Instead of obtaining the intermediate product, a dark purple solid resulted. It was very sparingly soluble in hot water, and colored the solution pink only after prolonged boiling. It is readily soluble in solutions of the alkalies giving a deep purple solution from which it is precipitated by acids. It is probably a mixed phthalein.



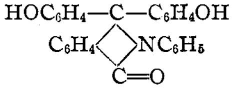
The results given in this paper can only be explained by assuming that phenolphthalein oxime has a structure similar to that of phenolphthalein imide and phenolphthalein anilide, substances formed from phenolphthalein and ammonia or from phenolphthalein and aniline, just as the oxime is formed from phenolphthalein and hydroxylamine.



Phenolphthalein oxime



Phenolphthalein imide



Phenolphthalein anilide

That these two substances do not undergo reduction or hydrolysis as readily as the oxime is easily explained because they do not undergo the Beckmann rearrangement as the oxime does. It is the intermediate product formed by the Beckmann rearrangement of the oxime that in reality undergoes the reduction and the hydrolysis. The objection that has been made to this formula by R. Meyer that it does not explain the color of the compound may be answered by calling attention to the fact that although phenolphthalein is a colorless substance to the naked eye, it has two absorption bands in the ultraviolet. Phenolphthalein oxime also has two absorption bands in the ultraviolet and apparently the effect of substituting the <NOH group for oxygen is the shifting of one of these bands towards the visible part of the spectrum. A small part of the blue is cut out and hence the solution appears yellow to the eye. Attention should also be called to the fact that phenolphthalein oxime, like the imide and anilide of phenolphthalein, dissolves in solutions of alkalies without under-

going the change into the quinoid condition so characteristic of phenolphthalein.

## Summary

The results obtained in this work may be briefly summarized as follows.

1. It has been shown that phenolphthalein oxime undergoes the Beckmann rearrangement when acetylated or benzoylated. The triacetate and dibenzoate formed are derivatives of the *p*-hydroxyanilide of *p*-hydroxybenzoyl-*o*-benzoic acid and not of the oxime.

2. The intermediate product (*p*-hydroxyanilide of *p*-hydroxybenzoyl-*o*-benzoic acid) has been isolated by saponification of its triacetate made from the oxime both with sulfuric acid and with dilute solutions of the alkalies.

3. It has been shown that the intermediate product undergoes hydrolysis when heated with dil. sulfuric acid, just as the oxime does, into *p*-hydroxybenzoyl-*o*-benzoic acid and *p*-aminophenol and the yield of both products is practically quantitative.

4. When reduced with zinc dust and dil. sulfuric acid the intermediate product gives the same reduction product that the oxime does.

5. When heated with a solution of hydroxylamine hydrochloride the intermediate product gives *p*-hydroxyphthalanil and phenol just as the oxime does.

6. When acetylated the intermediate product gives the same triacetate that is formed when the oxime is acetylated.

7. When benzoylated by the Schotten-Baumann reaction the intermediate product gives a dibenzoate, identical with that obtained from the oxime by the same treatment. Attempts to make the tribenzoate of the oxime described by R. Meyer and Kissen were unsuccessful.

8. The intermediate product gives a *colorless* trimethyl ether, when methylated in alkaline solution with dimethyl sulfate, isomeric with the *yellow* trimethyl ether obtained from the oxime by the same treatment.

9. Attempts to make the intermediate product synthetically from *p*-hydroxybenzoyl-*o*-benzoic acid and *p*-aminophenol were unsuccessful. A mixed phthalein was obtained instead.

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