The Constitution of Phenolphthalein Oxime

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Phenolphthalein oxime is shown to be a derivative of 2,3,1-benz-oxazine and not one of phthalimidine as hitherto assumed.

The oxime undergoes rearrangement and hydrolysis to *p*-hydroxybenzoyl benzoic acid and *p*-aminophenol not only in acid solution (as known) but also in alkaline solution.

N-methyl hydroxylamine reacts with phenolphthalein in alkaline solution similarly to hydroxylamine proper while *O*-methyl hydroxylamine does not react at all.

It is suggested that phenolphthalein hydrazide contains a six-membered heteroring instead of the hitherto supposed five-membered ring.

The similarity of the rearrangement of phenolphthalein oxime and that of triphenylmethyl hydroxylamine is pointed out.

Friedländer¹, in 1893, described a reaction between phenolphthalein and hydroxylamine in alkaline solution:

in which a yellow compound, named phenolphthalein oxime, was formed. It was at first supposed to be a quinone oxime:

The free oxime was insoluble in water, soluble in alkali and in dilute sulfuric acid. On boiling, the yellow solution in sulfuric acid gradually lost its colour and from the solution an almost quantitative yield of *p*-hydroxybenzoyl benzoic acid and *p*-aminophenol, 1 mole of each from 1 mole of the oxime, could be obtained. Friedländer interpreted this hydrolysis in the following way:

The primarily formed, then unknown, phenylhydroxylamine was supposed to rearrange into *p*-aminophenol.

Later ², however, he observed that tetrabromo phenolphthalein oxime — with bromine in the four *ortho*-positions to the phenolic hydroxyl groups — under similar conditions gave a dibromo *p*-aminophenol with bromine still in *ortho* positions to the phenolic hydroxyl group and so he had to abandon the quinone oxime hypothesis.

Several investigators ³ have discussed the constitution of phenolphthalein oxime and the conclusion generally accepted seems to be that the compound has the following structure:

It must be mentioned, however, that Thiel and Diehl ^{3a} do not feel entirely satisfied: »Es wird nach dem hier Gesagten sich als nötig erweisen, für das Oxim in jedem der besprochenen Zustände eine besondere Konstitutionsformel aufzustellen, eine Aufgabe, die angesichts der hier herrschenden, sicher sehr komplizierten Verhältnisse wohl nicht ganz leicht wird.» Their doubt is mainly caused by the different colour of the substance at pH 10 (orange) and pH 13 (pure yellow) and the fact that 3',3''-dinitro and higher nitrated phenolphthaleins do not form oximes.

Buu-Hoï ⁴, in 1940, suggests for the oxime of phenol-dimethylaniline-phthalein the quinone oxime formula for the primarily formed product which by recrystallization from alcohol is rearranged into the more stable heterocyclic form:

There are, however, several facts which are incompatible with the accepted formula I.

1. Phenolphthalein imide, formed from phenolphthalein and ammonia, has undoubtedly the constitution

but it is insoluble in dilute acids. It seems, therefore, quite improbable that a compound with the constitution I should be more basic than the imide.

2. Phenolphthalein oxime, when treated in alkaline solution with dimethyl sulfate, yields a yellow trimethyl ether which in boiling alcoholic potassium hydroxide splits off one methyl group ^{3b}. As methoxyl amine is stable to hydrolysis by alkali it appears unlikely that the $>\text{NOCH}_3$ group should be saponifiable.

Furthermore, the dimethyl ether obtained by acidifying the alkaline solution is yellow and readily soluble in ethyl ether. On short standing, however,

the ethereal solution deposits colourless crystals which are only slightly soluble in ether. When redissolved in alkali the yellow modification of the dimethyl ether again is formed when the solution is made acid. Obviously two forms of phenolphthalein oxime dimethyl ether exist and formula I does not account for this possibility.

3. Phenolphthalein, in alkaline solution, does not react at all with methoxyamine, H_2NOCH_3 . A solution has been kept for hours on a boiling water bath without any reaction occurring.

Against the quinone oxime formulation, besides the fact already mentioned, tells the reaction to be described later in this paper between phenolphthalein and N-methyl hydroxylamine which leads to quite similar products.

Thus the necessity of another formula for phenolphthalein oxime is evident.

As methoxyamine does not react with phenolphthalein it must be assumed that the hydroxyl group is involved in the condensation reaction. In neutral or only slightly alkaline solutions, *e. g.* phenolphthalein in an alcoholic solution of free hydroxylamine, no reaction takes place.

When an aqueous alkaline solution of phenolphthalein is brought to the "fading equilibrium" at room temperature, hydroxylamine added, and the solution placed in a spectrophotometer the absorption maximum of the red solution (at $552 \text{ m}\mu$) at first can be seen to decrease rapidly and after a while the decrease is far slower. The obvious explanation is that the coloured divalent phenolphthalein anion reacts fairly rapidly with hydroxylamine and soon the reverse of the fading reaction determines the rate of reaction:

At higher temperatures hydroxylamine apparently also reacts with the faded ion.

Since the reaction proceeds most rapidly in strongly alkaline solution it seems reasonable to assume that it is the hydroxylamine anion, H_2NO^- , that reacts with the phenolphthalein anion, the reaction being then quite similar to the fading reaction with hydroxyl ions:

and the constitution of the product obtained on acidification consequently is supposed to be

It is here assumed that the red phenolphthalein anion has the constitution of an amphi-ion. Usually a quinone-phenolate structure is ascribed to this ion; but it seems to me that the amphi-ion structure gives a better picture as it brings out the perfect symmetry of the two phenolic groups. Of course some resonance structure results from the ionization process and the formulation is only a suitable way of illustrating the essential properties. Moreover, in a recent paper Davies and Jones⁶ have shown that the infrared spectrum of the red phenolphthalein salts contains no "quinone frequencies".

The heteroring system assumed here to exist in the phenolphthalein oxime molecule — 2,3,1-benzoxazine — apparently has never been assigned to any existing compound so it cannot be inferred from analogous compounds whether or not such a substance might possess base properties. It appears, however, reasonable. The fact that the trimethyl ether has one saponifiable methyl group tends to show that the ether is derived from structure III, the grouping $\text{—C(OCH}_3\text{)=N—O—}$ being a modified hydroximic acid ester. The relatively high acidity of the oxime — it can be dissolved in potassium carbonate solution — is explained in the same way. The different colour of the solutions at different degrees of alkalinity depends on the different ionization — whether one has to do with a monovalent or a trivalent anion. The reason why the polynitro phthaleins do not form oximes is that the nitrophenolates do not effect ionization at the central carbon atom: their colour is the usual colour of nitrophenols in alkaline solutions.

The easy conversion of the yellow dimethyl ether to the colourless one is explained as a rearrangement of the dimethyl ether of III into that of II.

For further investigation of the reaction between phenolphthalein and hydroxylamine the latter was replaced by N-methyl hydroxylamine. To an alkaline solution of phenolphthalein was added the equivalent amount of N-methyl hydroxylamine and the mixture was kept at 60–70°. After 5–10 minutes the violet-red colour had disappeared and was replaced by a blood-red colour, and on acidification a yellow compound was precipitated. It contained nitrogen, but it has not been possible to obtain a pure product because a suitable solvent for recrystallization could not be found. — On longer standing of the reaction mixture at 60–70° the red colour faded considerably. After an hour the solution was made acid with acetic acid and an almost colourless compound slowly crystallized out. Obviously a rearrangement had taken place. The product obtained could be identified as the *p*-methylanilino-phenol salt of *p*-hydroxybenzoyl-*o*-benzoic acid.

In the alkaline solution thus were found products entirely analogous to the products of acid hydrolysis of the oxime proper. This fact of course invited to an examination of the oxime in alkaline solution, and it could be shown that a similar hydrolysis could be effected, although considerably slower. The oxime was dissolved in a hot aqueous solution of potassium carbonate and kept at 90° for 12 hours in a well stoppered flask. Addition of acetic acid caused a slow crystallization of a light yellow substance. (The oxime is precipitated instantaneously on acidification, and none was found; the oxime was completely transformed.) The product was, as expected, the *p*-aminophenol salt of hydroxybenzoyl benzoic acid.

These reactions throw light upon an observation made by Friedländer and others in connection with the preparation of phenolphthalein oxime: When

an excess of hydroxylamine is used the oxime is accompanied by a small amount of a byproduct which could be identified as *N*-(*p*-hydroxyphenyl) phthalimide.

Orndorff^{3f} assumed the formation of this compound to be due to the splitting off of a molecule of phenol from a rearranged form of the oxime, the reaction in some way being catalyzed by hydroxylamine:

It is, however, difficult to see any reason for such a reaction, and it has been possible to show that a second molecule of hydroxylamine is involved in the reaction and *p*-aminophenol is formed. When phenolphthalein (10 g) in alkaline solution was heated to 90° for one and a half hour with two equivalents of hydroxylamine 1.3 g of the phthalimide derivative and 0.4 g of *p*-aminophenol could be isolated besides 8 g of the oxime.

REARRANGEMENT OF PHENOLPHTHALEIN OXIME

The formation of *p*-hydroxybenzoyl benzoic acid and *p*-aminophenol from the oxime obviously implies a rearrangement of the oxime prior to the hydrolysis:

The same rearrangement also precedes the reaction with a second molecule of hydroxylamine:

It is necessary to assume that this reaction takes place before the rearrangement product IV is hydrolyzed because *p*-hydroxybenzoyl benzoic acid does

not react with hydroxylamine in alkaline solution: After two hours at 90° the acid could be recovered almost quantitatively.

The oxime dissolved in a solution of sulfuric acid in alcohol is reduced by zinc to the compound ^{3a,c,f}.

This reaction also must occur *after* rearrangement, but *before* hydrolysis.

The intermediate compound IV (or V) can, as shown by Orndorff, ^{3f} be obtained by acetylating the oxime with acetic anhydride with subsequent hydrolysis of the triacetate.

While the trimethyl ether of the oxime can be boiled for any length of time with acetic anhydride without rearrangement the dimethyl ether when boiled in acetic anhydride for one or two minutes is rearranged, but not acetylated.

The product obtained in this way is insoluble in alkali.

The rearrangement of phenolphthalein oxime is somewhat similar to the Beckmann rearrangement: an organic radical migrating from carbon to nitrogen. It also recalls the transformation of triphenylmethyl hydroxylamine into benzophenone anil discovered by Stieglitz ⁶. As triphenylmethyl hydroxylamine is supposed to be a N-derivative one might consider the possibility of phenolphthalein oxime having the structure

Against this hypothesis the following objections can be made: (1) The non-reactivity of methoxylamine; (2) the observation made by Stieglitz that triphenylmethyl N-methylhydroxylamine only with great difficulty and with extremely low yields can be rearranged while by phenolphthalein N-methyl oxime the rearrangement proceeds even more readily than by the simple oxime, and (3) the saponification of the trimethyl ether.

In fact, the question arises if not the trityl hydroxylamine hitherto regarded as a N-derivative really is an O-derivative. In an excess of trityl chloride hydroxylamine forms a di-trityl hydroxylamine and it seems, on sterical grounds, very unlikely that a N-ditrityl hydroxylamine can be formed since ammonia is unable to form a ditritylamine. Furthermore, benzaldehyde

when heated with trityl hydroxylamine gives an oxime which has been assigned the formula $(C_6H_5)_3C \cdot N:CH \cdot C_6H_5$, but just as well might be O-trityl

benzaldoxime. In fact, the same compound is obtained from benzaldoxime sodium on treatment with trityl chloride.

If, on the other hand, trityl hydroxylamine is an O-derivative the Stieglitz transformation taking place in the presence of phosphorus pentachloride in an anhydrous solvent becomes quite analogous to the rearrangements found in the phenolphthalein oxime group:

PHENOLPHTHALEIN HYDRAZIDE

Hydrazine reacts with an alkaline solution of phenolphthalein with formation of a hydrazide⁷. In the literature the constitution of this substance is given as VI

It seems, however, more reasonable to assume the formation of a sixmembered ring VII or VIII. The compound is insoluble in dilute strong acids, so a free amino group is improbable. It seems to exist in two forms: The compound obtained by acidification of the alkaline solution in which it is formed is readily dissolved in warm acetic acid, but when the solution is brought to boiling it crystallizes out and is now sparingly soluble in acetic acid. It can be brought back to the soluble form again by dissolving it in alkali and acidifying the solution.

The two modifications probably correspond to the structures VII and VIII. They have the same melting point, but long before melting the crystals turn red, indicating some inner rearrangement of unknown nature.

EXPERIMENTAL

Phenolphthalein oxime

The oxime was prepared according to the procedure of Orndorff and Yang^{3f}.

Crystalline salts with sulfuric, hydrochloric, and perchloric acids are readily prepared by dissolving the oxime in warm (60–70°) dilute acids and cooling. The hydrochloride is sparingly soluble even in hot water and is best obtained by the addition of a little hydrochloric acid to a solution of the sulfate or perchlorate. They are all yellow. The oxime is recovered unchanged by addition of sodium acetate to aqueous solutions of the salts.

The only solvent dissolving considerable amounts of the oxime seems to be pyridine (or alkylpyridines). Addition of alcohol to such a solution precipitates the oxime in a very pure state, m.p. 216°.

Rearrangement of the oxime in alkaline solution. 15 g of the oxime are dissolved in a boiling solution of 5 g of potassium carbonate in 100 ml of water. The flask is then stoppered tightly in order to avoid oxidation from the atmosphere and is kept at 90° overnight. The still hot solution is acidified with acetic acid (10 ml in 50 ml of water). No precipitate is formed immediately, indicating that no unchanged oxime remains, but on cooling a light yellow crystalline substance separates. After half an hour the compound is filtered off and washed with cold water. Yield 14 g, m.p. after recrystallization from alcohol 200–01°. When recrystallized from water the substance is brownish-grey due to oxidation. (Found: C 68.2; H 4.90; N 4.08; 4.09. Calc. for $C_{20}H_{17}O_5N$: C 68.3; H 4.84; N 3.99).

From the reaction mixture strong acids precipitate directly *p*-hydroxybenzoyl benzoic acid and from the filtrate potassium carbonate precipitates *p*-aminophenol. The product formed in the process thus is the aminophenol salt of hydroxybenzoyl benzoic acid.

Phenolphthalein oxime ethers

The trimethyl ether was prepared and saponified according to Orndorff and Yang. The yellow dimethyl ether has m.p. 176–78°^{3b}. It dissolves readily in ether, but after a few minutes the yellow colour of the solution has faded and colourless crystals appear. The compound is now only slightly soluble in ether and melts at 156–57°. (Found: N 3.91. Calc. for $C_{22}H_{19}O_4N$: N 3.88).

Rearrangement. 5 g of the dimethyl ether in 10 ml of acetic anhydride was heated to boiling for 1–2 minutes and poured into water. As the acetic anhydride became hydrated a crystalline compound separated. The colourless compound after recrystallization from alcohol had m.p. 171–72°. (Found: C 73.1; H 5.41; N 3.90. Calc. for $C_{22}H_{19}O_4N$: C 73.2; H 5.31; N 3.88).

The product is insoluble in alkali and is supposed to be *p*-anisoyl-*o*-benzoic *p*-aniside or its cyclic isomer.

When treated similarly with diethyl sulfate phenolphthalein oxime yields a triethyl ether which can be saponified by alcoholic potassium hydroxide to a diethyl ether, a yellow compound, m.p. 157–58°. This ether retains its yellow colour when crystallizing from ethyl ether. (Found: N 3.62. Calc. for $C_{24}H_{23}O_4N$: N 3.59).

After treatment with acetic anhydride in the same manner as the dimethyl ether a snow-white compound is obtained, m.p. 201–02°, when recrystallized from alcohol. (Found: C 73.8; H 6.00; N 3.60. Calc. for $C_{24}H_{23}O_4N$: C 74.0; H 5.96; N 3.59).

The substance is insoluble in alkali and quite similar to the methyl compound described above.

Phenolphthalein and N-methyl hydroxylamine.

20 g of phenolphthalein and 7 g of N-methyl hydroxylammonium chloride are dissolved in a solution of 20 g potassium hydroxide in 80 ml of water. The solution is kept in a stoppered flask in a water bath at 65–70°.

In about 10 minutes the violet-red colour of phenolphthalein had disappeared and was replaced by a blood-red colour. A sample was taken out, diluted and acidified with acetic acid. A yellow substance separated, very soluble in alcohol, methanol, acetic acid and acetone, insoluble in non-polar solvents. No solvent suitable for recrystallization was found. Evaporation of alcohol from a solution left a glassy brick-red mass. The nitrogen content was too low, apparently due to an admixture of unreacted phenolphthalein.

The main portion was kept at the temperature mentioned for an hour when dilute acetic acid (20 + 80 ml) was added. The solution was now light yellow and no precipitate appeared at once. On standing for half an hour with occasional scratching and stirring 19 g of light greyish-yellow crystals were filtered off and washed with dilute alcohol and water. It was dried in an exsiccator protected against light. When exposed to sunlight the crystals become salmon-coloured.

The dry substance melts with decomposition at 125–27°. (Found: N 3.64; 3.65. Calc. for $C_{22}H_{21}O_5N$: N 3.69).

When the reaction mixture is made acid with strong acids *p*-hydroxybenzoylbenzoic acid is precipitated. *p*-Methylaminophenol was not isolated, but the filtrate when made alkaline rapidly darkened on exposure to oxygen, indicating the presence of this compound.

Phenolphthalein and excess of hydroxylamine

A solution of 10 g of phenolphthalein, 12 g of potassium hydroxide, and 5 g of hydroxylammonium chloride in 50 ml of water was kept at 90° for an hour and a half and then acidified with acetic acid. After cooling the precipitate was filtered off, washed with a little water and immediately treated with a solution of 20 ml conc. sulfuric acid in 150 ml water. The oxime dissolved, while *p*-hydroxyphenyl phthalimide could be filtered off. The oxime was set free with sodium acetate. The first mentioned filtrate was neutralized with potassium carbonate and *p*-aminophenol separated. Yields: 8.0 g of oxime; 1.3 g of imide, m.p. (from alcohol) 292–93°; 0.4 g of aminophenol, m.p. 185°.

To 1.3 g of the imide corresponds 0.7 g of aminophenol, but this compound is considerably more soluble in water than is the imide.

REFERENCES

1. Friedländer, P. *Ber.* **26** (1893) 174.
2. Friedländer, P. and Stange, A. *Ber.* **26** (1893) 2258.
- 3 a. Meyer, H. *Monatsh.* **20** (1899) 348.
b. Meyer, R. and Spengler, O. *Ber.* **36** (1903) 2964.
c. Meyer, R. and Kissin, S. M. *Ber.* **42** (1909) 2825.
d. Meyer, R. and Glikin, J. *Ber.* **40** (1907) 1454.
e. Orndorff, W. R. and Murray, R. R. *J. Am. Chem. Soc.* **39** (1917) 689.
f. Orndorff, W. R. and Yang, S. T. *Ibid.* **45** (1923) 1926.
g. Oddo, B. and Curti, D. *Gazz. chim. ital.* **54** (1924) 572.
h. Thiel, A. and Diehl, R. *Sitzber. Marburg Akad.* **62** (1927) 471.
4. Buu-Hoi, Ng. P. *Compt. rend.* **211** (1940) 209.
5. Davies, M. and Jones, R. L. *J. Chem. Soc.* **1954** 120.
6. Stieglitz, J. and Leech, P. N. *Ber.* **46** (1913) 2148; *J. Am. Chem. Soc.* **36** (1914) 283.
7. Orndorff, W. R. and Barrett, W. R. *J. Am. Chem. Soc.* **46** (1924) 2492.

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