mixed melting point determination with an authentic sample of triphenylboroxine showed no depression of melting point; yield of triphenylboroxine, 85%.

Isomerization of Tri-*sec*-butylboroxine.—Fifty grams (0.2 mole) of tri-*sec*-butylboroxine[7] was subjected to reflux under a 60-cm. column for 24 hr. Distillation gave only tri-*n*-butylboroxine, b.p. 242–243°, as shown by infrared spectrum.

Isomerization of Tri-*tert*-butylboroxine.—Fifty-three grams (0.21 mole) of tri-*tert*-butylboroxine,[7] m.p. 31°, treated substantially as described above, gave triisobutylboroxine. Three fractions boiled at 220–224°, $n^{25}D$ 1.4120–1.4123. The third fraction had d^{25} 0.8525 (lit.[7] $n^{25}D$ 1.4127, d^{25} 0.8540).

NOTRE DAME, INDIANA

[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY, THE UNIVERSITY OF CHICAGO]

Colorless and Yellow Forms of N-Hydroxyphthalimide

BY WILLIAM R. RODERICK[1] AND WELDON G. BROWN

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Contrary to a published report, the colorless and yellow forms of the compound known as "phthaloxime" have identical infrared spectra. Additional evidence is provided to show that the characteristic color and fluorescence of the yellow form is due to a trace impurity. The weight of evidence favors the N-hydroxyphthalimide structure.

The product from the reaction of phthalic anhydride with hydroxylamine, commonly known as "phthaloxime," has been described[2] as existing in two forms, colorless and yellow, but substantially identical in all other physical and chemical characteristics and as furnishing two series of derivatives likewise different only in color. Brady[3] proposed the term "xanthoisomerism" to describe this and other known examples of similar behavior. More recently, Mathis[4] reported a finding of substantial differences in the infrared spectra of the two forms and has renewed earlier efforts to assign to them radically different structures. His observations constitute the only evidence not reconcilable with a simpler explanation of the color—namely, that it is due to a difficultly separable impurity—and consequently we have re-examined the spectra.

We have found that the two forms of "phthaloxime" exhibit identical infrared spectra throughout the rock-salt region and, moreover, that the corresponding derivatives (acetates, methyl and benzyl ethers) are also indistinguishable by this means. The spectra (Table I), compared with known pairs of isomers having the phthalimide and isophthalimide structures, clearly support the N-hydroxyphthalimide structure.[5]

TABLE I

INFRARED ABSORPTIONS IN THE REGION 1700–1800 CM.$^{-1}$

N-Hydroxyphthalimide	1710sb[a]	1740sb	1787m
N-Methoxyphthalimide	.....	1735sb	1788m
N-Benzyloxyphthalimide	.....	1728sb	1788m
Phthalimide	.....	1735sb	1772m
Phthalanil	1708sb	1735m	1777w
Isophthalanil	1705sb	....	1785sb
			1795s,sh

[a] s = strong, m = medium, w = weak, b = very broad absorption; sh = shoulder.

Carpino,[6] having prepared an isomeric compound to which he assigns the isophthalimide type of structure on the basis of infrared comparisons and method of synthesis, likewise concludes that the compound under discussion here is N-hydroxyphthalimide.[7]

Our further observations relating to impurities in the yellow form are the following. Although the color could not be removed by crystallization procedures nor by means of ion-exchange chromatography, it could be partially removed by fractional vacuum sublimation or by solution in concentrated sulfuric acid followed by immediate precipitation by water. Complete removal was effected by chromatography of the acetate and by purification of the sodium or ammonium salts and regeneration of N-hydroxyphthalimide.[8]

Secondly, whereas the crude and initially colorless product from the reaction of phthalic anhydride with hydroxylamine can be converted to the yellow form, the purified product can no longer be converted by refluxing an acetic acid solution.[9] If, however, hydroxylamine is added to the purified product, the conversion to the yellow form is again possible. Finally, the N-methoxy- and N-benzyloxyphthalimides prepared from the yellow form became progressively less colored upon repeated crystallization; the N-benzyloxyphthalimide in particular was obtained in an essentially colorless form although it could still be differentiated from that derived from colorless N-hydroxyphthalimide by its ultraviolet-excited fluorescence. It is concluded that the reaction mixture contains a precursor, rather easily eliminated from the crude product by recrystallization, that is converted on heating to the persistent contaminant responsible for

(1) Monsanto Chemical Co. Fellow, 1956–1957.

(2) W. R. Orndorff and D. S. Pratt, *Am. Chem. J.*, **47**, 89 (1912).

(3) O. L. Brady, L. C. Baker, R. F. Goldstein and S. Harris, *J. Chem. Soc.*, 529 (1928).

(4) F. Mathis, *Bull. soc. chim. France*, [5] **20**, 797 (1953).

(5) D. E. Ames and T. F. Grey, [*J. Chem. Soc.*, 3518 (1955)], have reported the resemblance of the infrared spectrum of "phthaloxime" to that of N-ethylphthalimide and of the ultraviolet spectrum to that of phthalimide.

(6) L. A. Carpino, THIS JOURNAL, **79**, 98 (1957).

(7) Carpino's designation of the new isomer as "phthaloxime," while logically supportable, is likely to prove confusing in view of the extensive literature in which N-hydroxyphthalimide is referred to as phthaloxime. It seems preferable to drop the term "phthaloxime," the compounds under discussion being named as derivatives of phthalimide.

(8) Conversion of the yellow form to the colorless form has been effected by formation of the acetate, hydrolysis by aqueous ammonia and regeneration of N-hydroxyphthalimide from the ammonium salt.[2]

(9) The failure to confirm isolation of the yellow form, reported by L. Bauer and S. V. Miarka [THIS JOURNAL, **79**, 1983 (1957)] is consistent with this observation.

the color. This conclusion is in harmony with the observation that if the mother liquor from the reaction mixture is heated after isolation of the first crop the second crop is the yellow form.

The strong fluorescence exhibited by the yellow form in the solid state when excited by ultraviolet light provides a more sensitive criterion for the presence of the impurity than does the yellow color seen under ordinary illumination. As Orndorff and Pratt also noted,[2] the yellow color of the crystalline material is primarily a fluorescence effect. From our observations that the fluorescence is excited most intensely by incident light of 395 mμ wave length, it is inferred that the impurity possesses an absorption band at this wave length.

Solutions of the two forms (the solutions are not fluorescent) show no differences in the ultraviolet spectra below 350 mμ; the ultraviolet maxima are given in Table II. The spectra (Fig. 1) are very

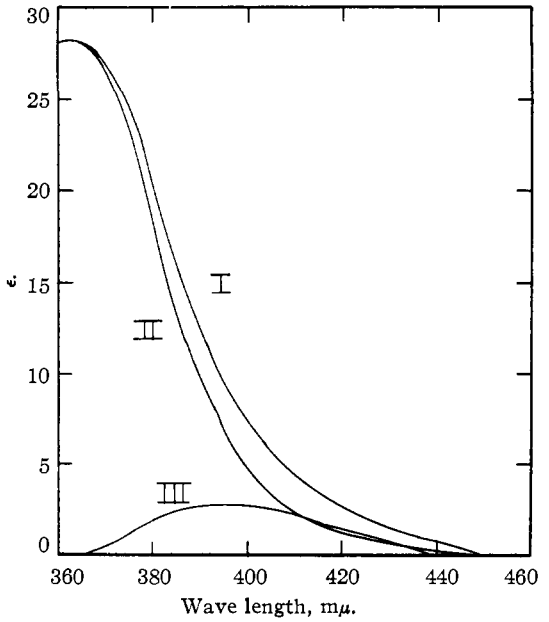

Fig. 1.—Long wave length absorption of N-hydroxyphthalimide in absolute ethanol: I, yellow form; II, colorless form; III, differential absorption (I minus II).

similar with weak absorption in the region 350–450 mμ (maximum at 360 mμ), but the yellow form shows a distinctly greater absorption, with the difference, yellow minus colorless, maximal at 395 mμ. This difference persists in acidic solutions and is thus not due to traces of the salts, which show a broad maximum at 425 mμ. Due to the intense absorption of the anion (derived from either form) the absorption of solutions is highly *p*H-dependent above *p*H 4, and it is probable that the differences in spectra (250–320 mμ) of solutions reported by Brady[3] were due to differences in the *p*H of the solutions being compared.

If the substance responsible for the yellow color is assumed to have a value of ϵ (395 mμ) not greater than 5×10^4, the lower limit for its abundance is fixed by the observed spectral differences at about 5 parts in 10^5 parts of N-hydroxyphthalimide. The actual concentration may be somewhat higher but in any case it is low enough to discourage attempted isolation in quantities sufficient for identification. Of the efforts made in this direction, the most promising is the observation that chromatography of the acetate leaves a substance on the column as a blue-white fluorescent zone after elution of the acetate.

TABLE II

ULTRAVIOLET ABSORPTIONS

Compound	Solvent	λmax, mμ	
N-Hydroxyphthalimide	Abs. ethanol	≤220	25,700
		293	1,700
N-Hydroxyphthalimide	Dist. water	≤220	8,200
		280	1,200
N-Hydroxyphthalimide	1 *N* hydrochloric acid	230	7,400
		275	1,200
	N,N'-Dimethylformamide	293	1,800
N-Methoxyphthalimide	Isoöctane	≤220	42,700
		239	13,700
		289	1,800
N-Methoxyphthalimide	Abs. ethanol	≤220	35,400
		293	1,600
Sodium salt of N-hydroxyphthalimide	95% ethanol	≤220	18,200
		300	1,200

Experimental[10]

Preparation of Colorless N-Hydroxyphthalimide.—The colorless form was prepared by the method of Orndorff and Pratt[2] (reaction of phthalic anhydride with hydroxylamine in aqueous solution); colorless, non-fluorescent needles, m.p. 219.5–223.5° dec. (sealed tube) (lit.[2] 220–226° dec.).

Preparation of the Yellow Form of N-Hydroxyphthalimide. A.—Yellow N-hydroxyphthalimide was prepared according to the method of Orndorff and Pratt[2] by refluxing a solution of the crude colorless form in glacial acetic acid. The products ranged from pale yellow needles with slight yellow fluorescence to bright yellow needles with strong fluorescence; m.p. 216.5–221.5° dec. (sealed tube).[11]

B.—When a reaction mixture from the preparation of colorless N-hydroxyphthalimide (containing precipitated N-hydroxyphthalimide) was heated for several hours at 60°, the product was still colorless. However, when the suspended N-hydroxyphthalimide was separated and the filtrate refluxed for one hour, the second crop was bright yellow with strong fluorescence; m.p. 211–213° dec. (sealed tube).

C.—Recrystallized colorless N-hydroxyphthalimide was added to a warm solution of an equivalent amount of potassium acetate in glacial acetic acid; an equivalent amount of hydroxylamine hydrochloride was added, and the solution was refluxed for one hour. After decantation from the potassium chloride, the solution was cooled; orange, non-fluorescent crystals formed which gave a positive test for hydroxylamine, presumably present as the salt of N-hydroxyphthalimide. After being washed with acetic acid, yellow crystals were obtained with yellow fluorescence, m.p. 212–215° (sealed tube), and infrared spectrum identical with that of N-hydroxyphthalimide. While the visible color was not as intense as that of the yellow form prepared in A or B, the yellow fluorescence was equally intense.

Removal of the Yellow Color. A.—Sublimation of a sample of light yellow (light yellow fluorescence) N-hydroxyphthalimide at 110° (2 mm.) yielded colorless, non-fluorescent N-hydroxyphthalimide. Similar treatment of a strongly colored sample (strong yellow fluorescence) yielded a pale yellow sublimate with strong yellow fluorescence; on resublimation the product was even less colored but still had rather strong fluorescence.

B.—Yellow N-hydroxyphthalimide was dissolved in a minimum amount of warm concentrated sulfuric acid and

(10) All melting points have been corrected.

(11) Since the observed melting behavior of N-hydroxyphthalimide was irregular, variations in the region 210–225° are not significant.

immediately precipitated by the addition of water. (Longer standing in solution caused hydrolysis.) The white precipitate was washed until neutral and recrystallized twice from ethanol to give very pale yellow needles (pale yellow fluorescence) of N-hydroxyphthalimide.

C.—While chromatographic purification of the yellow form of N-hydroxyphthalimide was unsuccessful, this method was effective with the less polar N-acetoxyphthalimide. The acetates from both forms are colorless,[12] but the acetate from yellow N-hydroxyphthalimide has a strong bluish-white ultraviolet-excited fluorescence, while that from the colorless form does not fluoresce. When the acetate from the yellow form was chromatographed on silicic acid–Celite (3:1), it became non-fluorescent; a bluish-white fluorescent band remained on the column, but nothing could be isolated from this band.

D.—Aqueous ammonia was added to a solution of yellow N-hydroxyphthalimide in hot 95% ethanol. The precipitated ammonium salt was separated, dissolved in a minimum amount of water, and ethanol was added. On cooling the solution, a crystalline salt formed; it was separated and the recrystallization repeated. The orange crystals were then dissolved in a minimum amount of cold water and the solution acidified with dilute hydrochloric acid. The precipitate was washed to remove acid and recrystallized from ethanol to give colorless, non-fluorescent needles.

N-Benzyloxyphthalimide.—This derivative, hitherto incompletely characterized,[5] was prepared from both the colorless and yellow forms of N-hydroxyphthalimide by treatment of the silver salts with benzyl chloride in dilute ether solution at room temperature for one week.[2] The products which separated upon concentration of the ether filtrate were fractionally crystallized to separate the mixture of regenerated N-hydroxyphthalimide and the desired benzyl derivative. The N-hydroxyphthalimide samples recovered from the two reactions were colorless and yellow, respectively. The yield of benzyl derivative in each case was 12%; the melting points separately were 143.0–144.5° in each case, on mixing, 143.0–144.0°.

Anal. Calcd. for $C_{15}H_{11}O_3N$: C, 71.13; H, 4.38; N, 5.53. Found: C, 71.03, 70.88; H, 4.51, 4.45; N, 5.15, 5.09. (The two figures in each instance refer to the product derived from colorless and from yellow N-hydroxyphthalimide, respectively.)

Preparation of Model Compounds.—Phthalanil was prepared by heating phthalanilic acid above its melting point. Isophthalanil was prepared by acetyl chloride dehydration of phthalanilic acid.[13] We were unable, following the procedure of Hoogewerff and van Dorp,[14] to prepare N-methylisophthalimide, desired as a second reference compound.

The infrared spectra of N-hydroxy-, N-methoxy- and N-benzyloxyphthalimide closely resemble the spectra of the normal phthalimides and are characterized by a broad and very intense absorption at about 1735 cm.$^{-1}$ and a sharp band of moderate intensity in the vicinity of 1790 cm.$^{-1}$. Isophthalanil has similar absorptions in this region, but they appear with approximately equal intensity and width.

(12) The pale yellow acetate from the yellow form, described by Orndorff and Pratt,[3] could not be obtained; presumably the yellow color was due to incomplete acetylation.

(13) M. L. Sherrill, F. L. Schaeffer and E. P. Shoyer, THIS JOURNAL, **50**, 474 (1928).

(14) S. Hoogewerff and W. A. van Dorp, *Rec. trav. chim.*, **13**, 98 (1895).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE FLORIDA STATE UNIVERSITY]

Cuprous Ion Formation in Cupric Ion Catalyzed Oxidations[1,2]

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The specific cuprous ion complexing reagent, cuproin, was used to explore the extent and mechanism of some cupric ion catalyzed oxidations. The cupric ion catalyzed oxidation of ascorbic acid is inhibited by cuproin (2,2′-biquinoline). Sulfhydryl compounds, some phenols and certain reducing agents produced cuprous ions under the described experimental conditions. Kinetic studies of the reduction of cupric ion by hydroquinone reveal that the reaction is bimolecular over-all and monomolecular with respect to cupric ion. This suggests a free radical intermediate for the oxidized compound. No simple order is observed for the interaction between cupric ion and *p*-hydroxyanisole or cysteine.

Copper ion catalyzed oxidation reactions afford an outstanding example of a model system for studying enzymatic oxidations. Copper enzymes have been considered in several recent reviews[3,4] and included in a recent American Chemical Society Symposium.[5]

It has been suggested that cupric ion catalyzed oxidations proceed through a generalized two-step mechanism. For the extensively studied oxidation of ascorbic acid, the following steps have been inferred[6–8]

(1) ascorbate + $2Cu^{++} \longrightarrow$ dehydroascorbate + $2Cu^{+} + 2H^{+}$

(2) (a) $2Cu^{+} + 2H^{+} + {}^1/_2O_2 \longrightarrow 2Cu^{++} + H_2O$

(b) $2Cu^{+} + 2H^{+} + O_2 \longrightarrow 2Cu^{++} + H_2O_2$

In this system copper functions catalytically by transporting electrons, in the Cu^{I} state from the oxidizable substrate to oxygen. Both alternatives (a) and (b), are observed for reaction (2); reaction type (a) is observed in the enzymatic reaction involving ascorbic acid oxidase.[3] Reaction type (b) is observed for the cupric ion catalyzed oxidation.[3,4]

Evidence for the existence of the Cu^{I} intermediate was first presented by Barron, *et al.*,[9] who demonstrated the inhibition of ascorbic acid oxidation

(1) Presented in part at the Meeting-in-miniature of the Florida Section of the American Chemical Society, Tallahassee, May, 1956, and in part at the Miami Meeting of the American Chemical Society, April 10, 1957.

(2) This work was supported by a research grant A-146 to E. Frieden from the National Institute of Arthritis and Metabolic Diseases, Public Health Service. The authors are grateful to G. Edwin Lewis and Dr. Ernest Grunwald for many interesting discussions of the problem.

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(4) T. P. Singer and E. B. Kearney, "The Proteins," Vol. IIA, 1954, pp. 135–159.

(5) O. Hayaishi, *et al.*, Symposium on Enzymatic Activation of Molecular Oxygen, 53C–58C, abstracts of papers presented at Atlantic City, N. J., September 16–21, 1956.

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