[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLLEGE OF PHARMACY, UNIVERSITY OF ILLINOIS]

The Chemistry of N-Hydroxyphthalimide

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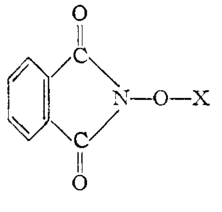
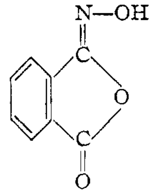
The structure and chemistry of "phthaloxime" or N-hydroxyphthalimide is discussed. In particular, the novel rearrangement of N-hydroxyphthalimide to anthranilic acid by benzenesulfonyl chloride in aqueous alkaline solution is reported.

The recent investigation of Ames and Grey[1] supports N-hydroxyphthalimide (Ia) as the structure of "phthaloxime," rather than the anhydride-oxime II[1a] which was proposed originally by Cohn.[2] Briefly, their evidence consisted in hydrogenolysis of N-benzyloxyphthalimide (Ie), which in turn was made by reaction of phthalic anhydride and O-benzylhydroxylamine, with the formation of "phthaloxime."



X

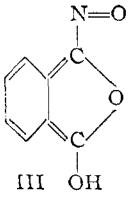
Ia, H
b, R
c, CH_3CO, C_6H_5CO
d, $C_6H_5SO_2$
e, $C_6H_5CH_2$



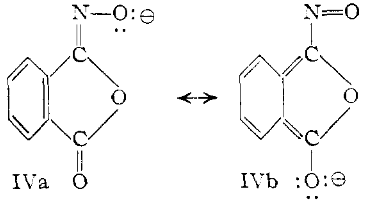
II

N-Hydroxyphthalimide has been synthesized by reaction of hydroxylamine with phthalyl chloride,[2] phthalic anhydride[3,4] or ethyl phthalate in the presence of sodium ethoxide.[5b] It is a weak acid (pK_a 7).[1] It forms highly colored orange to red salts with alkali metals, heavy metals, ammonia or amines. Its colorless ethers (Ib) undergo hydrolysis to O-alkylhydroxylamines, H_2NOR.[6] On acylation it yields acyl derivatives as Ic, Id.[7]

Although these reactions are accommodated by structure I, there are several points in the chemistry of N-hydroxyphthalimide that call for further study. For example, Orndorff[4] and Brady[6] claimed the isolation of a yellow isomer, with the same m.p. as Ia, following reaction of phthalic anhydride and hydroxylamine. This isomer was seemingly characterized by a series of yellow derivatives, isomeric with derivatives of the colorless series and of identical melting points. Mathis[8] assigned an *o*-quinonoid structure III for the yellow isomer. However, it has not been possible to confirm the isolation of the yellow isomer,[9] nor to convert Ia into a yellow isomer by refluxing in glacial acetic acid; colorless Ia was recovered.

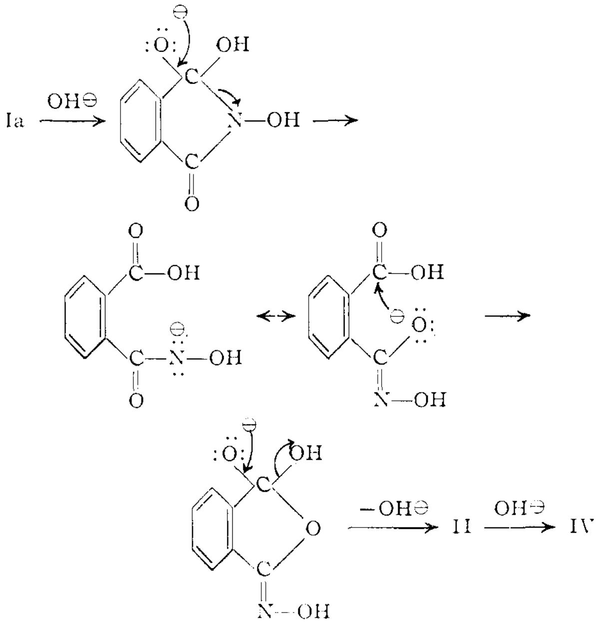


III

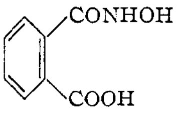


IVa IVb

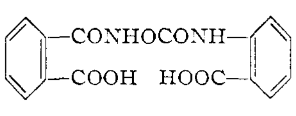
"Phthaloxime" forms a bright red anion. To explain this, it is postulated that the anion of "phthaloxime" is derived from structure II. The *o*-quinonoid–nitroso resonance hybrid IVb would account for the color satisfactorily, but there remains to be explained how it is formed from Ia since the latter structure seems well established generally. It is suggested that hydroxyl ion may cause ready isomerization of Ia to II as shown



These findings were obtained in the present study. In the synthesis of Ia from phthalic anhydride it was discovered that a crystalline hydroxylammonium salt of *o*-carboxybenzohydroxamic acid (V) was isolable as an intermediate by use of an excess of hydroxylamine at 25° in alcohol solu-



V



VI

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[1] D. E. Ames and T. F. Grey, *J. Chem. Soc.*, 3518 (1955).

[1a] ADDED IN PROOF.—L. A. Carpino [THIS JOURNAL, **79**, 98 (1957)] has recently synthesized and characterized II and reported it to be colorless and readily isomerized to Ia.

[2] L. Cohn, *Ann.*, **205**, 295 (1880).

[3] (a) B. Lach, *Ber.*, **16**, 178 (1883); (b) G. Errera, *Gazz. chim. ital.*, **24**, II, 469 (1894); (c) **25**, II, 25 (1895).

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

[5] (a) C. D. Hurd, C. M. Buess and L. Bauer, *J. Org. Chem.*, **17**, 856 (1952); (b) **19**, 1140 (1954).

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

[7] C. M. Buess and L. Bauer, *J. Org. Chem.*, **20**, 33 (1955).

[8] F. Mathis, *Bull. soc. chim.*, 797 (1953).

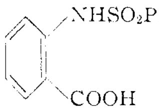
[9] C. M. Buess, private communication.

tion. Errera[3b] had reported this salt previously. This salt, which exhibited an intense purple color with ferric chloride solution characteristic of hydroxamic acids, was changed quantitatively into Ia on heating at 180° and 30 mm. Ia gives no ferric chloride color reaction. Reaction of the hydroxylammonium salt of V (in alcohol) with one equivalent of sodium ethoxide gave rise to the monosodium salt of V. This salt is new but the corresponding disodium salt of V is known.[5a]

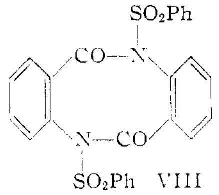
The behavior of Ia toward aqueous basic solutions was investigated. Under mild conditions not causing hydrolysis, as by use of cold 10% sodium carbonate solution, the acid dissolved to form a stable, red colored solution. Acidification regenerated colorless Ia. This is evidence for the equilibrium between Ia and II (or IV) that was postulated above. A similar result was obtained by use of the calculated amount of 5% sodium hydroxide solution, and acylation of this red solution with benzoyl chloride and benzenesulfonyl chloride yielded Ic, Id, respectively.

When an excess of aqueous sodium hydroxide or hot 10% sodium carbonate solution was used, then V was formed by hydrolysis. Its (V) presence was confirmed by the fact that it was colorless, that it tested positively with ferric chloride and that it underwent benzoylation to yield *o*-carboxybenzo-(benzoylhydroxamic) acid of known structure,[5a] quite different from Ic. The yield of this benzoyl derivative was brought to about 90% by adjusting the *p*H of the alkaline solution to 8 (with Dry Ice) before benzoylation.

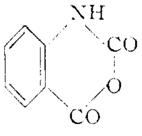
An alkaline solution of V was treated with benzenesulfonyl chloride to see whether it would undergo rearrangement to VI in the manner of other hydroxamic acids.[10] Actually, a variety of products was formed depending on conditions. No VI was isolable, but the anthranilic moiety of this molecule appeared instead in such compounds as the benzenesulfonic salt of anthranilic acid, the benzenesulfonyl derivative VII, the cyclic amide VIII and isatoic anhydride IX.



VII



VIII



IX

The benzenesulfonyl derivative Id also undergoes a Lossen rearrangement in alkaline solution[7] to produce a mixture of anthranilic acid and ethyl *o*-carboxyphenylcarbamate, $HOOCC_6H_4NHCOOC_2H_5$.

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Experimental

N-Hydroxyphthalimide. (a) From Phthalic Anhydride.—The preparation was essentially similar to that described.[4] The crude product melted at 227–230° and was used in the experiments described below. Recrystallization from water, acetic acid or 2-propanol raised the melting point to 233° (lit. value[1] is 232–233°). The bands in the carbonyl region were at similar wave lengths as described.[1]

(b) From Ethyl Phthalate.—To a solution of hydroxylamine (3.6 g., 0.11 mole) in ethanol (150 ml.) was added ethyl phthalate (22.2 g., 0.1 mole), followed by sodium ethoxide solution (2.3 g. of sodium in 50 ml. of ethanol). The temperature rose from 10 to 35°. The salt commenced to precipitate and was collected after four hours. It weighed 15 g. when dry.

On acidification of some of the salt (1.85 g.) N-hydroxyphthalimide (0.4 g.) was precipitated, m.p. 233°.

Hydroxylammonium Salt of *o*-Carboxybenzohydroxamic Acid.—Hydroxylammonium chloride (21.0 g., 0.3 mole) was dissolved in absolute methanol (100 ml.). A solution of sodium methoxide (6.9 g. of sodium in 150 ml. of methanol) was prepared. The two solutions were mixed at room temperature and the precipitated sodium chloride was filtered off. To the methanolic hydroxylamine solution was added powdered phthalic anhydride (15 g.) and the solution allowed to stand overnight. Colorless crystals deposited which were filtered off and washed with cold methanol. The yield of the salt was 17 g. (81%). The salt was sparingly soluble in hot methanol, hot ethanol, insoluble in hot tetrahydrofuran. The m.p. was a function of the rate of heating and the apparatus used. In a capillary tube, the material changed color about 130° and melted 188–189°. On an electrically heated hot-stage, between cover slips, the m.p. was observed at 233°. An aqueous solution of the salt, on acidification, gave an intense purple color with ferric chloride solution.

For analysis the salt was crystallized from methanol. It formed colorless rhombs.

Anal. Calcd. for $C_8H_{10}N_2O_5$: C, 44.85; H, 4.70; N, 13.08. Found: C, 44.24; H, 4.45; N, 12.90.

The infrared spectrum (in KBr) showed continuous intense absorption between 2703 and 3077 cm.$^{-1}$. The absorption between 1400 and 1700 had a number of bands, notably at 1661 (carbonyl group of –CONHOH) and a doublet at 1600 and 1587 cm.$^{-1}$ (ionized carboxylate).

Action of Heat on the Hydroxylammonium Salt of *o*-Carboxybenzohydroxamic Acid.—The salt (200 mg.) was heated at 180° and 30 mm. pressure for 45 minutes. The pale cream residue melted at 230° (hot-stage). Its infrared spectrum was identical with that of N-hydroxyphthalimide.

Sodium *o*-Carboxybenzohydroxamate.—When powdered phthalic anhydride (0.1 mole) was added to a stirred solution of hydroxylamine (0.125 mole) in ethanol (200 ml.), some of the above hydroxylammonium salt commenced to precipitate. Sodium ethoxide (0.1 mole) in ethanol (70 ml.) was added to the heterogeneous medium. Sodium *o*-carboxybenzohydroxamate separated as a finely divided powder and was filtered off after an additional 0.5 hour of stirring. The yield of the dry salt was 17 g. (85%).

This salt was used for benzoylation and rearrangement experiments described below.

N-Benzoyloxyphthalimide.—Sodium N-hydroxyphthalimide (prepared from ethyl phthalate) (1.85 g.) was dissolved in water (10 ml.) and benzoyl chloride (1.4 ml.) added. The mixture was shaken and the temperature kept between 5 and 10°. Sodium hydroxide solution was added at various intervals to keep the solution just alkaline. After 30 minutes, more benzoyl chloride (0.3 ml.) was added. The product was filtered after 45 minutes, washed with water and dried. It weighed 2.05 g. Recrystallization from ethanol afforded colorless rhombs, m.p. 174–175°. The m.p. in the literature[5b] is 168–169°.

The infrared spectrum (in Nujol) was marked for its lack of absorption in the 3 μ region, a very weak band at 1832, medium band at 1800, strong bands at 1770, 1735 and another weak band at 1602 cm.$^{-1}$.

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[10] (a) C. D. Hurd and L. Bauer, This Journal, **76**, 2791 (1954); (b) M. A. Stolberg, R. C. Tweit, G. M. Steinberg, and T. Wagner-Jauregg, *ibid.*, **77**, 765 (1955).

***o*-Carboxybenzo-(benzoylhydroxamic) Acid.**—This acid had been prepared previously from disodium *o*-carboxybenzohydroxamate.[5a] Schotten–Baumann benzoylation of the monosodium salt (prepared above) gave the benzoylhydroxamic acid, m.p. 157–158° (from ethyl acetate). The m.p. recorded[5a] is 159–160°.

This benzoyl derivative may be prepared directly from N-hydroxyphthalimide: N-Hydroxyphthalimide (6.4 g.) was dissolved in ice-cold 10% sodium hydroxide solution (110 ml.). Dry Ice was added until the *p*H was lowered to about 8. Benzoyl chloride (7.0 ml.) was added to the vigorously stirred solution (15 minutes). After 20 minutes, a test portion, when acidified, gave no color with ferric chloride. The reaction mixture was acidified with concentrated hydrochloric acid, the solid filtered off and dried *in vacuo*. The solid was refluxed with a mixture of benzene (75 ml.) and petroleum ether (37 ml.) for 10 minutes. After cooling, the derivative was filtered and redried. The m.p. was 150°, the yield 10.6 g. (93%) based on N-hydroxyphthalimide.

The infrared spectrum in KBr showed a strong band at 3175 (combined OH and NH stretching frequencies) and in the carbonyl region, strong bands at 1779, 1667 (due to $-CONHOCOC_6H_5$) and at 1689 cm.$^{-1}$ (C=O stretching vibration) of the COOH group.

N-Benzenesulfonoxyphthalimide.[7]—The infrared spectrum (in Nujol) showed no absorption in 3 μ region. In the carbonyl region, there was a very weak band at 1817, a medium band at 1795, a very strong band at 1745 and two weak bands at 1610 and 1585 cm.$^{-1}$.

Rearrangement of N-Hydroxyphthalimide with Benzenesulfonyl Chloride. (a) **Preparation of Anthranilic Acid.**—N-Hydroxyphthalimide (3.2 g., 0.02 mole) was dissolved in ice-cold sodium hydroxide solution (5 g. of sodium hydroxide in 50 ml. of water). The transient red salt initially formed dissolved immediately to give a colorless alkaline solution of *o*-carboxybenzohydroxamic acid (intense purple color with acidified ferric chloride solution). Benzenesulfonyl chloride (3 ml., *i.e.*, 4.2 g., 0.025 mole) was added dropwise to the stirred solution over a period of 5 minutes. The temperature rose from 4 to 9° within the first ten minutes. The mixture was stirred altogether 40 minutes (negative ferric chloride test).

Excess benzenesulfonyl chloride was extracted with low-boiling petroleum ether. The alkaline solution was acidified with concentrated hydrochloric acid and then an aqueous benzenesulfonic acid solution (15.8 g. in 20 ml. of water, 0.1 mole) was added. The mixture was chilled and scratched. Anthranilic acid benzenesulfonate crystallized in colorless needles. The product was filtered, washed with a little ice-cold 5 *N* hydrochloric acid. When dry, the salt weighed 3.9 g., m.p. 226–228°. The acid mother liquor was evaporated to dryness *in vacuo* and the solid residue extracted repeatedly with absolute ethanol (3 portions of 75 ml. each). The alcoholic solution was evaporated to dryness and the solid triturated with a little ice-cold water. An additional quantity (0.4 g., m.p. 232°) of anthranilic acid benzenesulfonate could be obtained that way. The total yield was then 4.3 g. or 75% based on N-hydroxyphthalimide.

The salt was recrystallized from absolute ethanol giving needles, m.p. and mixed m.p. with an authentic specimen[11] 235°. The authentic specimen was prepared by mixing a hot aqueous solution of anthranilic acid with an excess of benzenesulfonic acid and allowing the product to crystallize.

The infrared spectrum of the salt showed strong broad absorption between 2941 and 3125 (OH and NH stretching vibration) and a strong sharp band at 1718 cm.$^{-1}$ (C=O of COOH group).

The salt (1.45 g.) was dissolved in hot water (7.5 ml.) and sodium acetate trihydrate (4 g.) was added. On cooling, anthranilic acid (0.5 g.) was obtained, m.p. 135–138°. Two recrystallizations raised the m.p. to 143–144°, undepressed by an authentic specimen.

(b) **Preparation of *o*-Benzenesulfonamidobenzoic Acid.**—N-Hydroxyphthalimide (3.2 g., 0.02 mole) was dissolved in an ice-cold sodium hydroxide solution (5.0 g. in 75 ml. of water). Benzenesulfonyl chloride (10.2 ml., *i.e.*, 14.2 g., 0.08 mole) was added dropwise in 30 minutes. The temperature rose from 0 to 20°. After 30 minutes the mixture was stirred at room temperature for 1.5 hr. Excess benzenesulfonyl chloride was removed by extraction with low-boiling hydrocarbon solvents. The alkaline solution was acidified and the solid collected. The yield of the sulfonamide was 4.5 g. (81% based on N-hydroxyphthalimide) and melted at 209–211°. Recrystallization from 50% aqueous ethanol raised the m.p. to 211–212°. Its m.p. was undepressed on admixture of an authentic specimen prepared from anthranilic acid and benzenesulfonyl chloride.[12]

The infrared spectra of the two benzenesulfonamido acids were superimposable. The main absorption bands were a broad band between 3000 and 3150 (OH and NH absorption), a strong band at 1675 (C=O of the COOH group). Strong bands, due to sulfonamide groups,[13] were located at 1095, 1165 and 1340 cm.$^{-1}$.

In a similar experiment, the *p*H of the solution was adjusted to 13 after 1 hr. by the addition of 10% sodium hydroxide solution. After 2 hr., there was present N,N′-dibenzenesulfonyldianthranil (0.5 g.), m.p. 245°. Several recrystallizations from glacial acetic acid yielded colorless rhombs, m.p. 264–265°. The recorded m.p. for this substance is 264°.[12]

The infrared spectrum of this compound (in Nujol) is noted for the absence of any bands at 3.0, one strong carbonyl band at 1695 cm.$^{-1}$.

Rearrangement of Sodium *o*-Carboxybenzohydroxamate with Benzenesulfonyl Chloride.—This rearrangement was similar to that of N-hydroxyphthalimide described above. The salt (4.1 g., 0.02 mole) was dissolved in ice-cold aqueous sodium hydroxide solution (4.5 g. of sodium hydroxide in 75 ml. of water). Benzenesulfonyl chloride (3 ml.) was added over a period of eight minutes. After 40 minutes, the mixture was extracted with pentane. The alkaline solution was acidified first with hydrochloric acid and then with benzenesulfonic acid (15.8 g.). Anthranilic acid benzenesulfonate (3.0 g.) was precipitated and the mother liquor when worked up as above afforded an additional 0.45 g. The total 3.45 g. represents a 58% yield based on the sodium salt.

If benzenesulfonyl chloride was added to the alkaline solution of V at 25° and the temperature not controlled, a mixture of base-insoluble materials was precipitated. A poor yield of isatoic anhydride (m.p. 236–237°, carbonyl bands at 1730 and 1780 cm.$^{-1}$) was found in some of these mixtures. Acidification of the basic mother liquors yielded a mixture *o*-benzenesulfonamidobenzoic acid and the benzenesulfonic acid salt of anthranilic acid.

CHICAGO 12, ILLINOIS

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[11] (a) Z. Foldi, *Ber.*, **55**, 1538 (1922); (b) G. Heller and H. Grundmann, *ibid.*, **56**, 205 (1923).

[12] (a) G. Schroeter, *ibid.*, **40**, 1610 (1907); (b) G. Schroeter and O. Eisleb, *Ann.*, **367**, 101 (1909).

[13] J. N. Baxter, J. Cymerman-Craig and J. B. Willis, *J. Chem. Soc.*, 669 (1955).