[Contribution from the Chemical Laboratories of
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p,p'-AZOXY- AND p,p'-AZO-DIBENZOIC ACIDS

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Recent studies in these laboratories of *in vivo* biochemical synthesis by *Neurospora crassa* when grown in the presence of critical concentrations of *p*-aminobenzoic acid (1, 2), made it necessary to compare certain of the metabolic products, both chemically and spectrally, with some oxidation products of *p*-aminobenzoic acid, *viz.*, *p,p'*-azoxy- and *p,p'*-azo-dibenzoic acid. However, a survey of the literature revealed various inconsistencies in the reported properties of these acids, occasionally even when prepared by different workers using essentially similar methods.

In the preparation of *p,p'*-azoxydibenzoic acid Loesner (3) and Vorländer (4) reduced *p*-nitrobenzoic acid (as the sodium salt) with sodium arsenite. Both obtained products that decomposed at high temperatures without melting; the latter described his material as "Supracrystalline". The recently described alkaline glucose reduction of *p*-nitrobenzoic acid (5) furnishes a product of m.p. 240° (dec.), and the same melting point is reported by Kirpal (6) who oxidized *p,p'*-azoxydibenzaldehyde with chromic acid. A melting point of 249–251° (dec.) is reported by Weisler and Helmkamp (7) who obtained their product from the basic hydrolysis (in air) of β-methoxy-β-(*p*-nitrophenyl)-α-phenylacrylonitrile. On the other hand the dimethyl ester of the azoxydiacid is consistently described as a crystalline compound melting at about 207° (7–9).

The preparation of pure *p,p'*-azodibenzoic acid also appears to be a matter of extreme complexity. Löb (10) reports it to be an orange-red powder when formed by the electrolytic reduction of *p*-nitrobenzoic acid. Carré (11) isolated his product from an alcoholic sodium hydroxide treatment of *p*-nitrobenzyl alcohol and describes it as red needles, decomposing at about 330° without melting, when recrystallized from acetic acid. Weisler and Helmkamp (7), from the basic hydrolysis of their nitrile in the absence of air obtained the azodiacid of melting point 330° (dec.). On the other hand, Bilfinger (12) states that the acid carbonizes at a high temperature "with the ejection of a yellow smoke." Meigen and Nottebohm (13), who oxidized *p*-aminobenzoic acid with hypobromite, report for their azodiacid the melting point 240° without decomposition. Very recently Mehta and Vakilwala (14) oxidized *p*-aminobenzoic acid with sodium perborate and claim for their azodibenzoic acid decomposition at 330°. The glucose reduction of *p*-nitrobenzoic acid at 50° is reported (15) to yield the azoxy derivative, while at 75° the azodiacid is supposed to form. These claims (15)

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have been disputed by Tomlinson (16) who reported that at either temperature mixtures of azo and hydrazo derivatives were formed.

In our hands several of the above reductive methods for the preparation of *p,p'*-azoxydibenzoic acid were completely unsatisfactory. Occasionally materials having melting points between 240 and 250° could be isolated from these reductions. Melting appeared mainly to be due to the presence of some unchanged *p*-nitrobenzoic acid. Other preparations refused to melt and only decomposed at high temperatures to give black residues. Proof of the impurity of these preparations was afforded by the fact that the dimethyl ester, prepared from the silver salt and methyl iodide, not only melted over a considerable range, but was separable chromatographically into several fractions *viz.*, the dimethyl esters of *p,p'*-azoxy- and *p,p'*-azo-dibenzoic acids, identical with specimens prepared by our standardized procedures, together with other unidentified material. It follows that the different preparations of the azoxydiacid reported by various workers appear to be due to the presence of some unreduced nitroacid together with azodiacid and other impurities, and it may be stated here that the same difficulties are responsible for the lack of consistencies attributed to preparations of the azodiacid.

Two different procedures were developed for the preparation of these two acids that successfully overcame these difficulties. By using the very mild reducing conditions afforded by potassium hydroxide in methanol, for extended periods, it was found that all of the nitroacid could be reduced to yield almost analytically pure *p,p'*-azoxydibenzoic acid. This material is a yellow powder, insoluble in all except basic organic solvents, decomposing only slowly at 400° and more rapidly at elevated temperatures. It may be transformed in almost quantitative yield into the dimethyl ester obtained by other workers.[3] On the other hand it appeared impossible to control more vigorous reductions so as to isolate pure azodibenzoic acid. The procedure finally standardized, therefore, utilizes very vigorous reduction to form the hydrazo derivative, which is then oxidized by means of air to form *p,p'*-azodibenzoic acid in yields over 80%. The material thus prepared is a pink powder, insoluble in all except basic organic solvents,[4] decomposing rapidly without melting, above 400°. It forms, in very high yield, the dimethyl ester described by Meyer and Dahlem (8), who prepared the compound by sodium amalgam reduction of methyl *p*-nitrobenzoate without isolation of the free acid.

Figure I reproduces the ultraviolet absorption spectra of the two acids and their dimethyl esters, the former in 0.1 *N* sodium hydroxide solution, the latter in 95% ethanol. Under these conditions the two acids (and esters) are easily distinguished. For *p,p'*-azoxydibenzoic acid two maxima appear: at 268 mμ (ϵ 11,700), and at 334 mμ (ϵ 18,400). For the dimethyl ester these are at 266 mμ (ϵ 14,300), and at 332 mμ (ϵ 21,600) (an additional maximum was located at *ca.* 226 mμ,

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[3] We wish to thank Professor R. W. Helmkamp of The University of Rochester for a specimen of dimethyl *p,p'*-azoxydibenzoate.

[4] Contrary to the report of Carré (7) who recrystallized his product from acetic acid to obtain red needles.

ϵ 20,200). For *p,p*'-azodibenzoic acid three maxima appear: at 225 mμ (ϵ 11,900), at 331 mμ (ϵ 25,600), and at *ca.* 430 mμ (ϵ 1,300). For the dimethyl ester these are at 226 mμ (ϵ 9,250), at 322 mμ (ϵ 30,100), and at *ca.* 427 mμ (ϵ 1,100). It may be noted that the oxidation of *p*-aminobenzoic acid with sodium perborate in acetic acid (14) is reported to form the azo diacid. Material prepared in this way by us contained an alcohol-soluble impurity, and, after exhaustive alcohol washes, had ϵ 21,000 for its absorption maximum at 331 mμ.

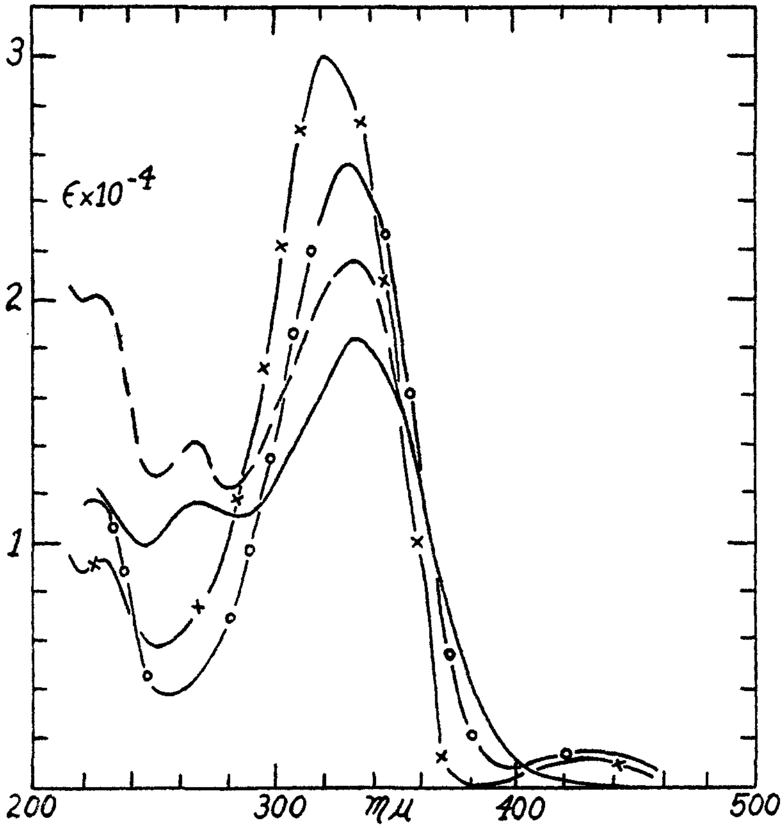

FIG. 1. ABSORPTION SPECTRA OF: ——— *p,p*'-azoxydibenzoic acid in 0.1 *N* NaOH; - - dimethyl *p,p*'-azoxydibenzoate in 95% ethanol; -o- *p,p*'-azodibenzoic acid in 0.1 *N* NaOH; - × - dimethyl *p,p*'-azodibenzoate in 95% ethanol.

EXPERIMENTAL

p,p'-Azoxydibenzoic acid. p-Nitrobenzoic acid (3.20 g., 0.021 mole), 15 g. of 85% potassium hydroxide (0.228 equivalent), and 150 ml. of absolute methanol were refluxed for 21 hours. At the end of this time the methanol was removed by distillation until a viscous orange-yellow residue remained. This was stirred with 150 ml. of water, filtered, and the remaining residue was discarded. The filtrate was adjusted to *p*H 7 with 10% hydrochloric acid and the resultant precipitate was collected and air-dried to a yellow powder. This material did not melt, but turned brown above 285°.

The yellow powder was dissolved in dilute ammonia and reprecipitated with hydrochloric acid. The precipitate was separated by centrifugation, washed with hot alcohol, and air-dried, forming a yellow powder which decomposed only slowly above 398°. Decomposition was almost explosive when a sample was heated on a spatula tip near a Bunsen burner. The solid refused to dissolve in a wide variety of neutral or acidic organic solvents. Yield: 1.80 g. (66%). The combustion analysis of this product revealed a trace of ash.

Anal.[5] Calc'd for $C_{14}H_{10}N_2O_5$: C, 58.74; H, 3.52.
Found: C, 58.85; H, 3.63.

Dimethyl p,p'-azoxydibenzoate. A toluene suspension of the di-silver salt, prepared by standard methods (17), was refluxed with excess methyl iodide for five hours. Evaporation of the resultant green toluene solution and recrystallization of the organic residue from methanol formed yellow crystals with shiny reflections, m.p. 204–205°. The yield of recrystallized product was 90% (from the silver salt). The same ester was obtained by treatment of the azoxydibenzoic acid with diazomethane in ether. The reaction was very slow, and the yield only 67% of recrystallized product. The mixture m.p. of each preparation with a specimen of dimethyl ester kindly furnished by Professor Helmkamp[3] was 204–205°.

Anal. Calc'd for $C_{16}H_{14}N_2O_5$: C, 61.14; H, 4.49; N, 8.91.
Found: C, 61.01; H, 4.46; N, 8.90.

p,p'-Azodibenzoic acid. p-Nitrobenzoic acid (1.668 g.) in 50 ml. of 30% aqueous sodium hydroxide was reduced at 80–85° with a 10% excess of zinc dust over that required to form the azoxy derivative (1.102 g., 90% zinc). When the zinc was nearly consumed, the mixture was diluted with 200 ml. of water and refluxed with a 25% excess of zinc dust over that necessary to convert the azoxy compound to the hydrazo derivative (0.922 g., 90% zinc). When the solution became almost colorless, it was allowed to cool slowly while air was bubbled through it.

The resulting azo salt precipitated slowly during three days, and was collected and dissolved in 300 ml. of water. Acidification of the salt solution with acetic acid precipitated the crude azo acid which was collected on a filter (filter aid) and washed with water and alcohol. The azo acid was then dissolved in dilute ammonia, filtered, and reprecipitated with acetic acid. The mixture was made 10% in hydrochloric acid and heated with stirring for 30 minutes on the steam-bath.

The product was then collected, washed with water, alcohol, and ether, and finally air-dried. The yield was 1.096 g. (81.2%), of pink powder, insoluble in various organic solvents including hot acetic acid[4] and 2-nitropropane. It darkened slowly at about 398°, and decomposed more rapidly at Bunsen flame temperatures (almost explosively) without melting.

Anal. Calc'd for $C_{14}H_{10}N_2O_4$: N, 10.37. Found: N, 10.28.

Dimethyl p,p'-azodibenzoate. This was prepared from the di-silver salt of the acid in benzene by essentially the method described above. The product formed red needles, m.p. 233–234° after recrystallization from methanol. This m.p. was raised to 236–237° [which is the m.p. reported by Meyer and Dahlem (8)], by passage of a benzene solution of the ester through a short column of alumina. The yield of product purified in this manner was 87% (from the silver salt).

Anal. Calc'd for $C_{16}H_{14}N_2O_4$: C, 64.42; H, 4.73; N, 9.39.
Found: C, 64.42; H, 4.54; N, 9.44.

Chromatographic separations. It was found possible to separate mixtures of the dimethyl esters of the azoxy and azo diacids on alumina, although neither ester was adsorbed very strongly. Thus, using the diester mixture (m.p. 206–216°) prepared from the product of a glucose-base reduction (15) of *p*-nitrobenzoic acid, chromatography on Fisher Adsorption Alumina (40–80 mesh) from benzene solution gave four bands. The top two bands were very small, and the lower two accounted for most of the material, equally distributed. The bands were cut away from the extruded column, and extracted with chloroform. Band 3 (yellow)

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[5] Our thanks are extended to Mr. Joseph Walter for the indicated analyses.

yielded yellow needles from chloroform-methanol, m.p. 204–206°, undepressed on admixture with methyl *p,p'*-azoxydibenzoate. Band 4 (orange) yielded reddish needles from chloroform-methanol, m.p. 237–238°, undepressed on admixture with dimethyl *p,p'*-azodibenzoate. Material present in bands 1 and 2 was not identified, nor was that obtainable from the white section of the column, between bands 2 and 3, identified.

It may be noted that reduction of *p*-nitrobenzoic acid directly to the azo stage with a 10% excess of zinc dust also yields a product contaminated with the azoxy derivative.

SUMMARY

Procedures have been developed for the preparation of either *p,p'*-azoxydibenzoic acid or *p,p'*-azodibenzoic acid in the pure state, by reduction of *p*-nitrobenzoic acid, and the ultraviolet absorption spectra of these acids and their methyl esters are recorded. The older procedures for these acids have been discussed and criticized.

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