Anal. Calcd. for $C_{26}H_{16}O_3$: C, 83.0; H, 4.3. Found: C, 83.1; H, 4.2.

α-(3-Phenthrylmethyl)-β-naphthoic Acid (VIII).—A mixture of acid VII (1.4 g.), zinc dust (5.0 g.) and 1 *N* potassium hydroxide solution (100 ml.) was refluxed for twenty-four hours. Removal of unused zinc and acidification gave a white solid. The material was crystallized three times from acetic acid; yield 0.65 g., m. p. 225°.

Anal. Calcd. for $C_{26}H_{18}O_2$: C, 86.2; H, 5.0. Found: C, 85.8; H, 5.4.

1,2,9,10-Dibenznaphthacene (II).—A mixture of VIII (0.65 g.) and zinc chloride (2 g.) was heated at 180–185° for thirty minutes. The reaction product was extracted with sodium carbonate solution and the residue, without isolating the anthrone, was refluxed for six hours with zinc dust (5.0 g.) and 1 *N* sodium hydroxide solution (250 ml.). The residue after filtration was extracted with acetone, the acetone evaporated and the hydrocarbon taken up in benzene and isolated as the dipicrate. Without any purification, the picrate melted at 217–219°. An equal-part mixture of the latter and the picrate from II made by pyrolysis showed no melting point depression. The dipicrate afforded 0.1 g. of yellow hydrocarbon, m. p. 248–250°. An equal-part mixture of the latter and II obtained by pyrolysis showed no melting point depression. The residue from the acetone extraction was extracted with benzene and xylene. No hydrocarbon could be detected in the extracts. The zinc residue was treated with hydrochloric acid and no hydrocarbon could be detected in the resulting almost negligible residue.

Acknowledgment.—We wish to express our gratitude to Mrs. J. H. Woods of Calgary, Alberta, who provided the funds without which this work would have been impossible. One of us (J. C. N.) wishes to express his indebtedness to the National Research Council of Canada for a special grant during the summer of 1945. The spectrographic work was supported by a grant from The Donner Foundation, and this is gratefully acknowedged. The authors also wish to thank Drs. C. B. Purves and J. M. Pepper for their kind assistance in the hydrogenation of phenanthrene.

Summary

1. The pyrolyses of 2-methyl-1-naphthyl-2′-(and 3′)-phenanthryl ketones and 2-methyl-1-naphthyl-2′-(9,10-dihydrophenanthryl) ketone have been investigated.

2. A possible synthetic proof for the structure of 1,2,9,10-dibenznaphthacene has been presented.

EDMONTON, ALBERTA, CANADA

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8-Nitrocinchoninic Acids and Related Substances[1]

BY EDWIN R. BUCHMAN, CHESTER M. MCCLOSKEY[1a] AND J. ALBERT SENEKER

In connection with the problem[2] of combining both quinine and Plasmochin features in the same molecule, feasible methods for obtaining 8-nitrocinchoninic acids and corresponding 8-amino derivatives were investigated; these studies were confined to three series.

In series a, 8-nitrocinchoninic acid (Ia) had previously been prepared[3] by nitration of lepidine and subsequent oxidation; this path afforded preparative access (see Experimental) to (Ia) which was isolated as the ethyl ester (IIa).

A suitable method for 2-phenyl-8-nitrocinchoninic acid (Ib) is not indicated in the literature. Its preparation from 7-nitroisatin (V) suggested itself since it had been shown[4] in this Laboratory that 5-nitroisatin could be used for a similar purpose. Although Borsche and co-workers[5] were not able to obtain nitroisatins by the Sandmeyer procedure, we encountered no difficulties in preparing (V) in this way. (V) reacted at 130° with acetophenone and aqueous ammonia[6] to give 2-phenyl-8-nitrocinchoninamide (VI) which was readily converted to (Ib).

In search for a more straightforward route to (Ib), the Doebner reaction was considered in spite of the fact that it had been reported[7] not to give (Ib). Recently it was shown by R. F. Brown and co-workers[8] that in the preparation of 2-(*p*-diethylaminophenyl)-cinchoninic acid from pyruvic acid, aniline and *p*-diethylaminobenzaldehyde in ethanol, the presence of a few drops of concentrated sulfuric acid in the reaction medium had a beneficial effect on the yield. Starting from this lead and after much varying of experimental conditions, we were able to work out a method which led directly from *o*-nitroaniline to (Ib). In its final form, our modified Doebner method was to allow approximately equimolar amounts of *o*-nitroaniline, benzaldehyde, anhydrous pyruvic acid and sulfuric acid to react spontaneously in the absence of the usual solvents; after a suitable

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[1a] Present address: Chemre Division, Alexander H. Kerr & Co., Los Angeles, California.

[2] Suggested by Johnson and Hamilton, ref. 10a; see also Turner and Cope, ref. 17.

[3] (a) Krahler and Burger, THIS JOURNAL, **64**, 2417 (1942); see also (b) Koenigs, *Ber.*, **31**, 2364 (1898).

[4] C. M. McCloskey, to be published.

[5] (a) Borsche, Weussmann and Fritzsche, *Ber.*, **57**, 1149 (1924); see also (b) Rupe and Stöcklin, *Helv. chim. acta*, **9**, 579, footnote (1926).

[6] *Cf.* Bayer and Co., German Patent 290,703 (Friedlaender, *Fortschr. Teerfarbenfabrikation*, **12**, 724); see also Petrow, *J. Chem. Soc.*, 18 (1945); also ref. 4.

[7] Borsche, *Ber.*, **41**, 3884 (1908).

[8] Brown, *et al.*, THIS JOURNAL, **68**, 2705 (1946).

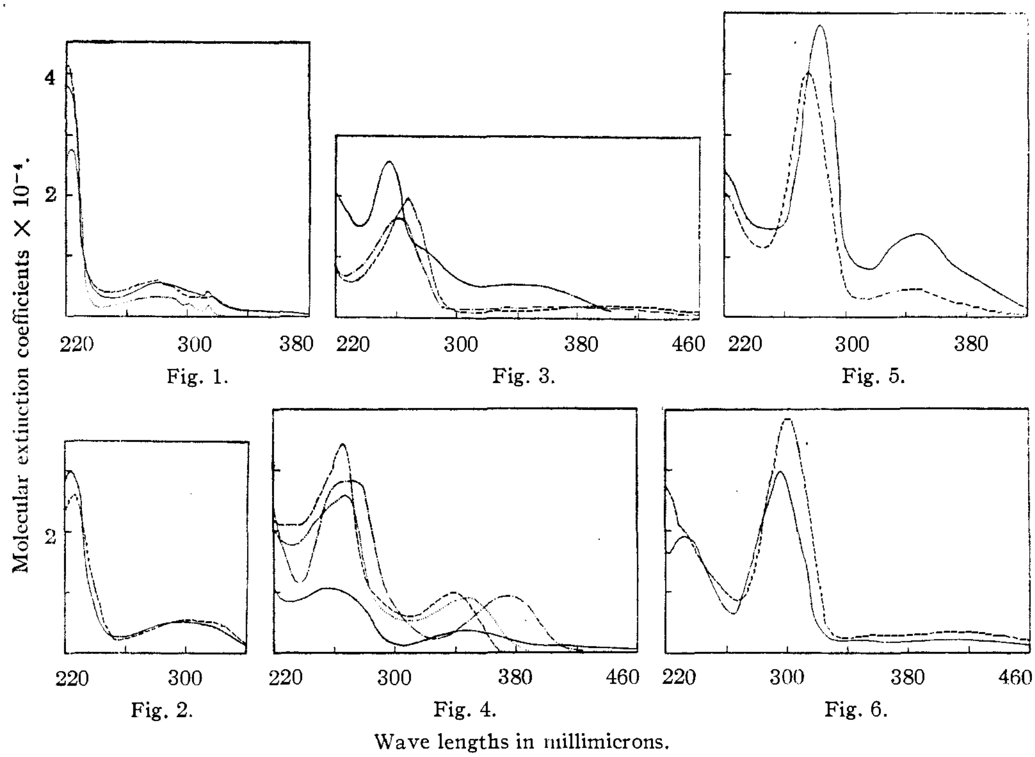

Fig. 1. Fig. 3. Fig. 5. Fig. 2. Fig. 4. Fig. 6.

Figs. 1–6.—The solvent was ethanol in all cases. Absorption maxima for lepidine were found at 224, 277, 301, 314 mμ (*cf.* Ward, *Biochem. J.*, **17**, 903 (1923)); $\lambda_{max.}$ values for the other substances are given in the Experimental.

Fig. 1.—.... Lepidine, — 8-nitrolepidine (VII), - - - x-nitrolepidine (VIII).

Fig. 2.—— 8-Nitrocinchoninic acid (Ia), - - - ethyl 8-nitrocinchoninate (IIa).

Fig. 3.—·— 8-Aminocinchoninic acid, - - - ethyl 8-aminocinchoninate (IIIa), — ethyl 8-benzamidocinchoninate (IX).

Fig. 4.—— 7-Nitroisatin (V), - - - 2-phenyl-8-nitrocinchoninamide (VI), ... ethyl 2-phenyl-8-nitrocinchoninate (IIb), —·— ethyl 2-phenyl-6-methoxy-8-nitrocinchoninate (IIc).

Fig. 5.—- - 2-Phenyl-8-hydroxycinchoninic acid, — ethyl 2-phenyl-8-hydroxycinchoninate.

Fig. 6.—— Ethyl 2-phenyl-8-aminocinchoninate (IIIb), --- ethyl 2-phenyl-6-methoxy-8-aminocinchoninate (IIIc).

working up procedure, ethyl 2-phenyl-8-nitrocinchoninate (IIb) was obtained in 34% yield (details see Experimental).

In series c, the substitution of 2-nitro-4-methoxyaniline for *o*-nitroaniline in the modified Doebner led similarly to the formation of 2-phenyl-6-methoxy-8-nitrocinchoninic acid (Ic).

Catalytic reduction of the 8-nitrocinchoninic esters (II) gave in good yield the corresponding 8-amino esters (III). In all three series it was noted that, while esters (II) are colorless or nearly so, the reduced compounds (III) are orange-red or red. In order to better document these relationships, the absorption spectra of these compounds are recorded (see chart).

Experimental[9]

8-Nitrolepidine (VII).—Following the procedure of Johnson and Hamilton,[10] but on a scale ten times that used by these authors, 650 g. of technical lipidine (Reilly Tar and Chemical Corporation) was nitrated (reaction temperature 0–3°), with the cooling bath at −15 to −20°; the addition of nitrating mixture required about two hours. After the addition, the temperature was held at 0° for one-half hour and the bath removed; as soon as the temperature reached 30–35°, the mixture was again cooled and maintained at 20–24° during a final stirring period of three hours. After pouring on ice, the product was precipitated by ammonia as an oil which crystallized on standing overnight. It was dissolved in 4.5 liters of ethanol; on standing and cooling, finally at 5°, two crops of crude (VII) were obtained which were recrystallized from ethanol; yield 372 g., m. p. 126–126.5° (lit.[10] m. p. 126°), $\lambda_{max.}$ 283, 314 mμ.

The mother liquors from crude (VII) were concentrated to 600 ml. After standing overnight at 5°, small yellow needles had crystallized which were filtered off and recrystallized from ethanol with application of charcoal, yield 72 g. This substance (VIII),[11] an isomer of (VII), crystallized from ethanol (considerably more soluble than (VII)) in light yellow needles, m. p. 127.5–129°, which darkened on exposure to light; $\lambda_{max.}$ 222, 278, 316 mμ.

Anal. Calcd. for $C_{10}H_8N_2O_2$: C, 63.82; H, 4.28; N, 14.89. Found: C, 63.90; H, 4.26; N, 14.92.

The combined mother liquors were concentrated and seeded, giving an additional 40 g. of (VII) (total yield of

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[9] All melting points are corrected; microanalyses by Dr. G. Oppenheimer and staff of this Institute and by Huffman Microanalytical Laboratories, Denver 2, Colorado. For the spectra recorded in this paper, we are indebted to Mrs. B. Dandliker and to Miss P. Baskett.

[10] (a) Johnson and Hamilton, THIS JOURNAL, **63**, 2864 (1941); see also (b) Busch and Koenigs, *Ber.*, **23**, 2687 (1890).

[11] Possibly identical with a compound isolated by Busch and Koenigs[10b] and described as gleaming yellow needles, m. p. 112°.

(VII) 48.2%) and from the filtrates (VIII) was isolated to bring the total yield of this isomer to 114 g. (13.3%).

Ethyl 8-Nitrocinchoninate (IIa).—To the stirred, refluxing solution of 200 g. (1.11 moles) of (VII) and 400 g. of anhydrous sodium acetate in 2 liters of glacial acetic acid, 380 g. (2.38 moles) of bromine in 1.5 liter of glacial acetic acid was added rapidly.[3] Refluxing was continued for five minutes; then the solution was allowed to cool, filtered and the filter-cake washed with glacial acetic acid. The filtrate and washings were combined and the solvent recovered by distillation *in vacuo* (solid which separated during distillation was filtered off to prevent bumping). After removal of solvent, the residue crystallized and was taken up in 1 liter of benzene plus 1 liter of water. The benzene layer was separated, the aqueous portion reextracted with 0.5 liter of benzene and the combined benzene extracts were freed of solvent *in vacuo*.

A solution of the product in 1800 ml. of 60% acetic acid (in a flask protected by a dark cloth from the light) was heated on the steam-bath to drive off remaining benzene. Then, to the hot, vigorously stirred solution (after removing the steam-bath) was added 360 g. (2.13 moles) of silver nitrate over a period of five minutes[3]; heating was resumed immediately thereafter. At the end of two hours, the remaining silver ions were precipitated with saturated ammonium chloride solution.[12] The silver salts were filtered off, washed with acetone and the filtrates combined and concentrated nearly to dryness. The residue was poured into 1 liter of ice water, neutralized to congo red with ammonium hydroxide and the precipitate filtered off and air-dried.[13]

A solution of this material in 4 liters of 50% aqueous pyridine was cooled to 0° and, with stirring, 100 g. of finely powdered potassium permanganate was added over forty-five minutes.[3] The solution was then allowed to warm to room temperature (three hours) and gaseous sulfur dioxide was passed in until the precipitate of manganese dioxide had dissolved. Solvent was recovered by evaporation to dryness under reduced pressure and the residue was thoroughly extracted with dilute aqueous ammonia. The extracts were neutralized to congo red and after standing overnight the yellow precipitate was filtered off, washed with water and air-dried; yield of crude 8-nitrocinchoninic acid (Ia) 160 g.; $\lambda_{\max.}$ (for purified (Ia)) 224, 293–296 mμ.

The crude acid was dissolved in 1.7 liters of ethanol containing 170 ml. of concentrated sulfuric acid and refluxed for fourteen hours. Three-fourths of the alcohol was distilled off *in vacuo* and the residue poured onto 3 liters of ice and water containing sufficient ammonia to neutralize the acid. The solid was filtered off, washed, air-dried, and refluxed with 3 liters of isopropyl ether for several hours. The solution was decanted from tar and cooled; a first crop of brownish crystalline (IIa) (m. p. 84°) was obtained and concentration of the filtrate afforded a second crop; the total yield was 115 g. (44% based on (VII)). Recrystallization from ligroin (60–70°) and then from isopropyl ether gave colorless crystals, m. p. 84–85°; $\lambda_{\max.}$ 226, 304 mμ.

Anal. Calcd. for $C_{12}H_{10}N_2O_4$: C, 58.53; H, 4.09; N, 11.38. Found: C, 58.25; H, 4.06; N, 11.17.

Ethyl 8-Aminocinchoninate (IIIa).—A suspension of 49.2 g. (0.2 mole) of (IIa) in 600 ml. of ethanol was shaken with 0.4 g. of platinum oxide in an atmosphere of hydrogen; three mole-equivalents of hydrogen were rapidly absorbed. After filtering and concentrating to dryness under reduced pressure, the residue was extracted by refluxing with three 800-ml. portions of ligroin (60–70°). The ligroin solution was treated with charcoal, filtered and, on cooling, long red-orange needles of (IIIa) crystallized out. Additional crops were obtained by concentrating mother liquors nearly to dryness and extracting with boiling ligroin as before; total yield 39.3 g. (91%). For analysis (IIIa) was recrystallized twice from ligroin (60–70°), m. p. 77.5–78°, $\lambda_{\max.}$ 267, (330), 400–401 mμ.

Anal. Calcd. for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.60; N, 12.96. Found: C, 66.62; H, 5.59; N, 13.11.

Saponification of (IIIa) gave 8-aminocinchoninic acid, which crystallized as dark red needles from alcohol, m. p. 280–281° (rapid heating, 271° on slow heating), $\lambda_{\max.}$ 262, 380 mμ (not reproducible); the hydrochloride of the acid is sparingly soluble in cold water.

Ethyl 8-Benzamidocinchoninate (IX).[14]—To a solution of 40 g. (0.185 mole) of (IIIa) in 100 ml. of dry pyridine was added 23 ml. (0.2 mole) of benzoyl chloride. The reaction mixture was stirred for ten minutes, diluted with 500 ml. of water and filtered. The precipitate was washed with water and air-dried; yield 57 g. (96%), m. p. 194–194.5°. For analysis (IX) was crystallized from butanone with no change in m. p.; $\lambda_{\max.}$ 255, 334, (348) mμ.

Anal. Calcd. for $C_{19}H_{16}N_2O_3$: C, 71.24; H, 5.04; N, 8.74. Found: C, 71.06; H, 5.19; N, 9.09.

Isonitrosoacet-*o*-nitroanilide (IV).[5a,15]—A mixture composed of 2 liters of water, 750 g. of technical anhydrous sodium sulfate and 108 g. (0.65 mole) of chloral hydrate was heated to 40° to obtain solution and a mixture of 90 g. (0.65 mole) of *o*-nitroaniline and 150 ml. of 12 *N* hydrochloric acid which had been triturated was added with stirring. A solution of 142 g. of hydroxylamine hydrochloride in 500 ml. of water was then added and the mixture, with vigorous stirring, heated rapidly to the boiling point (thirty-five minutes) and boiled for fifteen minutes. After cooling, the reaction mixture was filtered and the solid stirred with 1 liter of 5% sodium hydroxide for two hours and filtered again. (IV) was precipitated from the filtrate by acidifying with hydrochloric acid, filtered, washed with water, and air-dried, m. p. 142.5–143°; yield 65 g. (47.8%). An analytical sample obtained by taking up in isopropyl ether–ligroin (60–70°), filtering, evaporating solvent and recrystallizing from benzene, melted at 145.5–146° (lit.[5a] m. p. 142°), analysis for $C_8H_7N_3O_4$.

7-Nitroisatin (V).[15]—Finely powdered (IV) (65 g., 0.31 mole) was added with stirring to 650 ml. of concentrated sulfuric acid (heated to 80°) in a 2-liter flask; the temperature was kept at 95–100° for fifteen minutes by appropriate heating or cooling. The mixture was poured upon ice, allowed to stand for two hours, filtered and the product washed and dried; the yield was 40.7 g. (68%) of tan powder. Recrystallization from acetic acid (nitrobenzene was later found more expedient) gave an analytical sample, m. p. 232–233°, $\lambda_{\max.}$ 255–256, 346–349 mμ.

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(12) The addition of excess hydrochloric acid leads to oxidative side reactions.

(13) The product thus obtained contains considerable (Ia). A relatively pure aldehyde is precipitated by making the solution strongly alkaline with ammonia; after filtering, (Ia) can be recovered by neutralization of the filtrate to congo red.

(14) Preliminary attempts were made to convert 8-substituted cinchoninic esters to 8-substituted quinolyl-4 carbinols (Plasmochin-quinine analogs) by an Ainley and King type of synthesis (*Proc. Roy. Soc.* (London), **125B**, 60 (1938)). IIa, while stable to sodamide when refluxed with the latter in a benzene medium, gave tars when ethyl ε-benzamidocaproate (X) (supplied by Dr. C. C. Price, University of Illinois) was also added; after acid hydrolysis, no ε-aminoamyl ketone was isolated. IIIa in the presence of sodamide reacted vigorously with X in benzene to give an insoluble precipitate which was not hydrolyzed by refluxing with 6 *N* hydrochloric acid. Condensation of 1 equivalent each of IX, X and sodamide in benzene, followed by hydrolysis, gave no ketone; however, modified procedures, involving more than 1 equivalent of X gave some promise: A mixture of 13 g. (0.0406 mole) of IX, 25.6 g. (0.0975 mole) of X and 3.8 g. (0.0975 mole) of sodamide in 25 ml. of benzene was heated at 100° for twenty-four hours (in another experiment, excess of X was used as dilutent in place of benzene). After hydrolysis by refluxing with 6 *N* hydrochloric acid for twenty-four hours, the basic material in the solution was liberated and transferred first to chloroform and then to 48% hydrobromic acid. After evaporating to dryness *in vacuo*, the bases were again freed with ammonia, taken up in chloroform and solvent removed; a crystalline product was obtained on treating the residue with isopropanol.

(15) *Cf.* Marvel and Hiers in "Organic Syntheses," Coll. Vol. I, 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1941, p. 327.

Anal. Calcd. for $C_8H_4N_2O_4$: C, 50.00; H, 2.10; N, 14.58. Found: C, 49.79; H, 2.35; N, 14.80.

2-Phenyl-8-nitrocinchoninamide (VI).—A mixture of 15.6 g. (0.081 mole) of (V), 18 ml. (0.155 mole) of acetophenone and 80 ml. of concentrated aqueous ammonia was heated at 130° for eight hours in an autoclave with shaking.[6,16] The aqueous solution was decanted and the tarry product triturated, first with 300 ml. of ethanol and then with a little methyl cellosolve (ethylene glycol monomethyl ether); the insoluble material weighed 1.9 g. (8%). Recrystallization of a portion from methyl cellosolve containing a drop of water gave fine, faintly yellow needles, m. p. 274.5–275°, $\lambda_{\max.}$ 266–267, 340–343 mμ.

Anal. Calcd. for $C_{16}H_{11}N_3O_3$: C, 65.52; H, 3.78. Found: C, 65.48; H, 4.03.

Ethyl 2-Phenyl-8-nitrocinchoninate (IIb): (**a**) **From** (VI).—One-half gram of (VI) in 2 ml. of concentrated sulfuric acid was heated at 145° for three hours; this solution together with 20 ml. of ethanol was refluxed for four hours. After cooling overnight, the crystals which formed were filtered off and washed with isopropyl ether; yield 0.17 g. (31%). This material, after recrystallization from butanone, melted at 143–143.5° and gave no depression when mixed with a sample prepared *via* the Doebner reaction (see below).

(b) **From the Doebner Reaction.**—To a mixture of 17.25 g. (0.125 mole) of *o*-nitroaniline, 13.25 g. (0.125 mole) of benzaldehyde, and 11 g. (0.125 mole) of anhydrous pyruvic acid in a 500-ml. flask was added 7 ml. (0.130 mole) of concentrated sulfuric acid. A vigorous reaction took place immediately and external cooling was sometimes required to prevent the reaction from foaming over. The reaction mixture was allowed to stand for thirty minutes and was then beaten mechanically with 50 ml. of chloroform, 100 ml. of water and 50 ml. of concentrated ammonia until all of the solid was dispersed. The ammonium salt of the acid crystallized out in part and, after twenty minutes, this was filtered off and washed with a little chloroform and with water. The combined filtrates were diluted with 400 ml. of water, shaken well, and the chloroform layer separated and re-extracted with 600 ml. of water containing a little ammonia and some ammonium chloride (necessary to prevent emulsion formation). The aqueous layer and ammoniacal extracts were combined with the ammonium salt, a little ice added and the mixture acidified with hydrochloric acid. After standing several hours, the precipitate of crude (Ib) was filtered off and dried either in the air or by the concentration to dryness of an ethanolic solution. An analytical sample, prepared by recrystallization from glacial acetic acid, melted at 272–273°; the spectrum was similar to that of (IIb), $\lambda_{\max.}$ 264–266, 341 mμ.

Anal. Calcd. for $C_{16}H_{10}N_2O_4$: C, 65.37; H, 3.43; N, 9.52. Found: C, 65.15, H, 3.42; N, 9.47.

The crude acid was esterified by refluxing with a solution of 25 ml. of concentrated sulfuric acid in 200 ml. of ethanol for five hours. After allowing the solution to cool to room temperature overnight, crystalline (IIb) was filtered off and washed with a little isopropyl ether; the yield was 13.76 g. (34.2%). The ester crystallized from butanone as both light yellow needles and plates, m. p. 143–143.5°, $\lambda_{\max.}$ 268, 347 mμ.

Anal. Calcd. for $C_{18}H_{14}N_2O_4$: C, 67.07; H, 4.38; N, 8.69. Found: C, 67.22; H, 4.50; N, 8.67.

The use of solvents or other addenda in the above Doebner reaction is not recommended. When acetic acid (100 ml. per mole) was employed as a partial solvent, substantially the same yield was obtained as that described; however, doubling the size of the run decreased the yield. Alcohol as a solvent gave low yields; the use of aqueous alcohol gave somewhat higher yields; arsenic pentoxide did not substantially increase the yield. Table I illustrates the effect of a few variables on the reaction.

TABLE I

THE EFFECT OF VARIED SULFURIC AND PYRUVIC ACID CONCENTRATIONS ON THE PREPARATION OF (IIb) *via* THE DOEBNER REACTION

A 0.125 mole each of benzaldehyde, *o*-nitroaniline and pyruvic acid.
B 0.125 mole each of benzaldehyde, *o*-nitroaniline and 0.094 mole of pyruvic acid.
C 0.125 mole each of benzaldehyde, *o*-nitroaniline and 0.063 mole of sulfuric acid.
D 0.125 mole each of benzaldehyde, *o*-nitroaniline and 0.188 mole of sulfuric acid. Schiff base prepared previous to pyruvic acid addition. Reacted thirty minutes on a steam-bath.

Effect of sulfuric acid				Effect of pyruvic acid				
Sulfuric acid, mole	Yield, %			Pyruvic acid, mole	Yield, %			
	A^a	B^a	B^b		C^a	C^b	D^a	D^b
0.031	24.4							
.063	29.8^c	27.8	37	0.061	27.6	55.4		
.125	34.2	30.6	40.8	.094	27.8	37	28.7	38.3
.188	27.6	26.4	35	.125	29.8	29.8	27.8	27.8
.25	19.3	19.9	26.6	.186	31.4	21	27.4	18.4

^{a} Based on *o*-nitroaniline. ^{b} Based on pyruvic acid. ^{c} Doubling the size of this run gave a small increase in yield.

Ethyl 2-Phenyl-8-aminocinchoninate (IIIb).[17,18]—The reduction of 1 g. of (IIb) (0.1 g. of platinum oxide and 100 ml. of methanol) required twenty minutes. The solution of the product in 100 ml. of ligroin (60–70°) was concentrated to 40 ml. and, on cooling, an oil separated out which crystallized on standing overnight as long orange-red needles. The crystals were filtered off and the mother liquor concentrated to yield a second crop; total yield 0.8 g. (88%). (IIIb) was recrystallized twice from ligroin (60–70°) seeding the warm solution, m. p. 69–69.5°[17], $\lambda_{\max.}$ 231–232, 297, 343–348, 400–420 mμ.

Anal. Calcd. for $C_{18}H_{16}N_2O_2$: C, 73.95; H, 5.52; N, 9.58. Found: C, 73.85; H, 5.80; N, 9.64.

Ethyl 2-Phenyl-8-hydroxycinchoninate.—2-Phenyl-8-hydroxycinchoninic acid ($\lambda_{\max.}$ 276, 341–343 mμ) was prepared essentially as described by Doebner[19]; a 50% aqueous solution of pyruvic acid and 95% alcohol were substituted for the anhydrous materials without decreasing the yield. The addition of a few drops of concentrated sulfuric acid[8] increased the yield slightly. Esterification with ethanolic sulfuric acid gave a product which crystallized from isopropyl ether in yellow needles, m. p. 71–71.5°,[17] $\lambda_{\max.}$ 283–285, 347–348 mμ.

Anal. Calcd. for $C_{18}H_{15}NO_3$: C, 73.71; H, 5.16; N, 4.78. Found: C, 73.92; H, 5.32; N, 4.74.

Ethyl 2-Phenyl-6-methoxy-8-nitrocinchoninate (IIc).—To 21 g. (0.125 mole) of 2-nitro-4-methoxyaniline (Eastman), 13.25 g. (0.125 mole) of benzaldehyde and 12.5 ml. of glacial acetic acid was added, first 7 ml. (0.125 mole) of concentrated sulfuric acid and then, after allowing the well-stirred mixture to react for five minutes, 11 g. (0.125 mole) of anhydrous pyruvic acid. The mixture was placed on a steam-bath and heated for thirty minutes, stirring until the reaction became homogeneous.[20] The

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(16) An attempt to condense (V) with acetophenone in the presence of 33% aqueous potassium hydroxide gave an insoluble acid (compare analogous reaction of 5-nitroisatin[4]) which on esterification with ethanol and sulfuric acid yielded an ester, m. p. 129.5–130.5° from ethanol (Found: N, 7.85, 7.64).

(17) Turner and Cope, THIS JOURNAL, **68**, 2214 (1946), have prepared (IIIb) by another method; two forms of the ester were obtained. Ethyl 2-phenyl-8-hydroxycinchoninate (m. p. 87.5–88°, Turner and Cope; *cf.* m. p. 71–71.5°, this paper) apparently constitutes an analogous case.

(18) *Cf.* preparation of (IIIa).

(19) Doebner and Fettback, *Ann.*, **281**, 7 (1894).

(20) Slightly lower yields were obtained by combining the ingredients simultaneously and allowing the reaction to take place without employing external heating.

resulting sirup was largely dissolved in 150 ml. of chloroform, cooled to room temperature and extracted, first with 300 ml. of 3 *N* ammonium hydroxide and then with water containing a little ammonia. Crude Ic was isolated and esterified as described for the corresponding operations in series b; the yield of crude IIc was 10.2 g. (23%). IIc crystallized from butanone in long faintly yellow needles, m. p. 160–160.5°, $\lambda_{max.}$ 264–266, 372–373 mμ.

Anal. Calcd. for $C_{19}H_{16}N_2O_5$: C, 64.77; H, 4.58; N, 7.95. Found: C, 64.81; H, 4.42; N, 8.31.

Ethyl 2-Phenyl-6-methoxy-8-aminocinchoninate (IIIc).[18]—The reduction of 4 g. of IIc (0.2 g. of platinum oxide and 200 ml. of methanol) required twenty minutes; IIc went into solution and near the end of the reduction, IIIc began to crystallize out. After redissolving and filtering from catalyst, 2.6 g. of large red needles was isolated by cooling the filtrate; dilution with water gave a second crop; the total yield was 3.55 g. (96%). Recrystallization from ethanol gave material having the same m. p. as the crude, 120–120.5°, $\lambda_{max.}$ 299–302, (*ca.* 355), 410–412 mμ.

Anal. Calcd. for $C_{19}H_{18}N_2O_3$: C, 70.79; H, 5.63; N, 8.69. Found: C, 70.84; H, 5.36; N, 8.76.

Summary

Several syntheses of 8-nitrocinchoninic acids have been investigated.

For preparation of 2-phenyl-8-nitrocinchoninic acid, a modified Doebner reaction has been developed; by use of this method 2-phenyl-6-methoxy-8-nitrocinchoninic acid has also been made available.

Catalytic reduction of 8-nitrocinchoninic esters (colorless) gave 8-aminocinchoninic esters (colored).

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[CONTRIBUTION FROM THE BIOCHEMICAL LABORATORY, STATE UNIVERSITY OF IOWA]

The Mechanism of the Antioxygenic Synergism of Quinones and Quinols with Phosphoric Acid and other Acids in Fat Systems[1]

BY VINCENT P. CALKINS[2,3]

The stabilizing action of traces of phosphoric acid, when added to certain fats, has long been known.[4,5] More recently it was demonstrated[6] that this action depended on the simultaneous presence of tocopherols or other phenolic inhibitors or their quinones and apparently consisted in a shift of the quinol ⇄ quinone equilibrium to the left, toward the reductant. The mechanism of this action is all the more intriguing because, although acids are known to favor this shift, the traces of phosphoric acid which impart increased stability are too minute to change the hydrogen ion concentration of the medium. The purpose of this investigation was to elucidate the mechanism by which a combination of quinones (or quinols) with traces of phosphoric acid achieves a much greater antioxygenic effect than is possessed by either alone, and to apply any resultant principles to other systems.

The fat substrate used was the ethyl esters of lard fatty acids, prepared in the usual manner and dehydrated by heating on a steam-bath under vacuum. When quinone was added its concentration was always 0.02%; in a third system the ethyl esters contained 85% orthophosphoric acid in two concentrations, 0.09 and 0.045%, and, finally, in a phosphoric acid–quinone–lard ethyl ester system, four different concentrations of phosphoric acid were used, namely, 0.09, 0.045, 0.009 and 0.0002%.

Quinone and phosphoric acid were incorporated into the fat system in the following manner. The solid ethyl esters, removed from cold storage, were liquefied by heating them gently under nitrogen on a steam-bath. A definite amount, weighed into a 400-ml. beaker, constituted the blank sample. In a larger amount of the esters sufficient quinone was dissolved to make a 0.02% solution. A portion of this, of the same weight as the blank, became the quinone–ester sample and like amounts were added to each of several 400-ml. beakers containing the desired quantity of phosphoric acid that had been weighed out on a cover slip and placed on the bottom of the beaker; ester solutions and esters were added carefully so as not to disturb the acid on the cover slip.

The beakers were covered with watch glasses and placed in an air oven at 60°; the air was stirred. At intervals quantitative determinations were made of the content of peroxides[7] and of quinols.[8] Since peroxides interfere with the Emmerie and Engel test, quinol determinations could not be made when appreciable amounts of peroxides were present.

Figure 1 presents a comparison of the appearance and disappearance of peroxides over a period of 140 days in samples containing quinone or phosphoric acid or neither. Both 0.09 and 0.045% of phosphoric acid showed a definite but

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[1] The experimental data in this paper are taken from a dissertation submitted by Vincent P. Calkins to the Faculty of the Graduate College of the State University of Iowa in partial fulfilment of the requirments for the degree of Doctor of Philosophy, April, 1943. Presented in part before the Chicago Meeting of the American Oil Chemists Society, November 1, 1946.

[2] A part-time grant from Merck and Co. is gratefully acknowledged.

[3] Present address: Tennessee Eastman Corporation, Oak Ridge, Tennessee.

[4] E. W. Eckey, U. S. Patents, 1,982,907 (1934); 1,933,152 (1935).

[5] H. S. Olcott and H. A. Mattill, THIS JOURNAL, **58**, 2204 (1936).

[6] Calvin Golumbic, *Oil & Soap*, **19**, 181 (1942).

[7] R. B. French, H. S. Olcott and H. A. Mattill, *Ind. Eng. Chem.*, **27**, 724 (1935).

[8] A. Emmerie and C. Engel, *Rec. trav. Chim.*, **57**, 1351 (1938).