[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE POLYTECHNIC INSTITUTE OF BROOKLYN]

SYNTHESIS OF NAPHTHYLAMINONAPHTHOQUINONES

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Received September 17, 1952

Although substituted quinones are commonly known (1) to have biological, bactericidal, or fungicidal activity in many instances, there are few references in the literature to the activity of amine-substituted quinones. In the naphthoquinone series where the hydroxyquinones are represented by 2-hydroxy-1,4-naphthoquinone, there are three references to antibacterial activity of aminoquinone compounds. Sulfanilamido-1,4-naphthoquinone possesses activity against pneumococci, *Escherichia coli*, and the tubercle bacillus (2–5). 2-(4′-Methyl-2′-pyridylamino)-1,4-naphthoquinone and several of its analogs are active against oral bacteria (6). Buu-Hoï reports that 2-(2′-naphthylamino)-3-chloro-1,4-naphthoquinone possesses activity against the tubercle bacillus (7).

The purpose of this investigation was to synthesize a series of 2-(2′-naphthylamino)-1,4-naphthoquinones with substitutents in the amine moiety in order to make them available for biological testing (to be reported elsewhere). These new compounds were to be prepared by the reaction of a series of substituted 2-naphthylamines with 1,4-naphthoquinone. Although the addition of naphthylamines to 1,4-naphthoquinone has not been studied, the class reaction, addition of amines to quinones, dates from 1863 (8).

Two methods are available in the literature for the addition of amines to 1,4-naphthoquinone. Normally, an excess of 1,4-naphthoquinone is used to oxidize the initially-formed substituted naphthohydroquinone to the corresponding 1,4-naphthoquinone (9–11). Lucius and Brüning (12) have reported that only equivalent quantities in absolute ethanol are necessary if cerium (III) chloride or copper (I) chloride is used with atmospheric oxygen to oxidize the substituted 1,4-naphthohydroquinone.

In preliminary experiments these methods were investigated to determine their suitability for the 1,4-naphthoquinone-2-naphthylamine reaction. In the series of experiments using excess quinone as an oxidant, without a metal halide catalyst the effect of varying reaction conditions (time, solvent, use of the amine sulfate or acetate, and concentration) were studied but the results obtained were not duplicable and the product was obtained in only fair yield. On the other hand, the Lucius-Brüning procedure using cerium (III) chloride as the oxygen carrier gave from 70–80% yields of product in 2.5 hours reaction time. The reaction was somewhat slower in 95% ethanol. Therefore, the Lucius-Brüning method in absolute ethanol was used throughout.

The addition of 1-bromo-, 6-bromo-, and 6-acetylamino-2-naphthylamine was effected in 35–61% yield of recrystallized products. 1,6-Dibromo-2-naphthyl-

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amine reacted very slowly, but the addition of a catalytic amount of sulfuric acid increased the rate and gave a 43% yield of recrystallized product. 6-Nitro-2-naphthylamine, which was only slightly soluble in absolute ethanol, gave only a 3% yield based on starting quantities, but 59% of the amine was recovered. 8-Nitro-2-naphthylamine gave a notably impure crude and a purified product in 15% yield. When the reaction between 1-nitro-2-naphthylamine and 1,4-naphthoquinone was attempted, the desired product did not form. However,

TABLE I

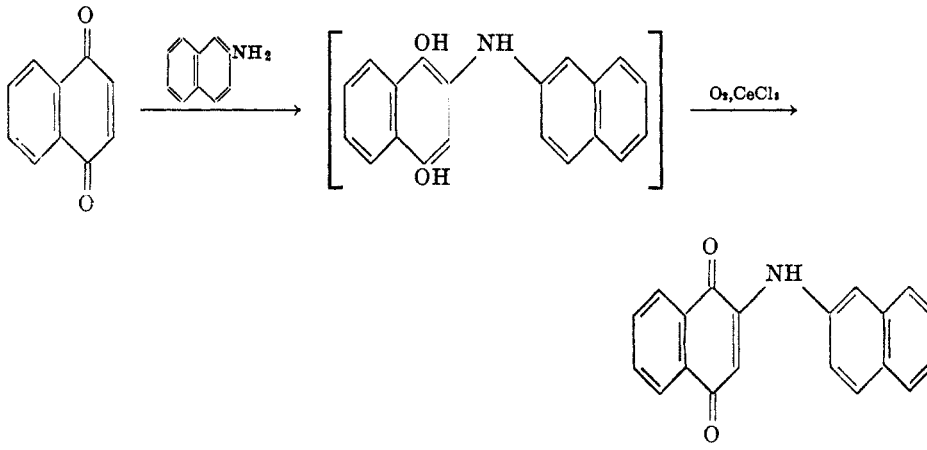
PREPARATION OF THE NAPHTHYLAMINONAPHTHOQUIONES

AMINE SUBSTITUENTS	FRACTION NO.	REFLUX (hrs.)	STAND[a] (days)	CRUDE PRODUCTS	
				Wt. (g.)	M.P. °C.
None	1	2.5	0	0.57	182–190
	2	2	1	.05	170–180
	3	0	12	.07	135–165
1-Bromo	1	2	1	.08	213–217
	2	2	1	.07	208–215
	3	0	4	.05	210–218
	4	8	7	.19	207–217
	5	12	6	.10	195–215
6-Bromo	1	1	0	.42	216–226
	2	1	1	.15	218–224
	3	3	1	.05	217–221
	4	0	4	.03	205–215
	5	2	1	.02	200–217
1,6-Dibromo	1	4	4	.15	80–150
	2	4	2	.15	242–246[b]
	3	2.5	8	.14	238–248
	4	6	5	.02	250–255
8-Nitro	1	2	0	.61	110–210
	2	0.5	2	.03	272–282
	3	2	2	.04	275–283

[a] One day of standing equals approximately 48 minutes of refluxing, see text. [b] Acid catalyzed.

using a catalytic amount of sulfuric acid, the product was obtained in 5% yield (recrystallized). Time did not permit further study of the favorable effect of acid catalysis.

The products were intensely colored varying from yellow-orange to purple-black. They showed low solubility in the usual organic solvents, but could be recrystallized from dilute solutions in benzene, lower aliphatic alcohols, or pyridine. Analysis showed them to be composed of one molecule each of amine and 1,4-naphthoquinone. Their formation is epitomized in the following equation:



The actual course of some of the experiments is shown in Table I. Although exact comparisons are not possible, it can be seen that, in general, the 6-bromo- and unsubstituted amines react faster than the 8-nitroamine which is more active than the 1-bromo- and 1,6-dibromo-amines. The 1-nitroamine was extremely unreactive. This order is that to be expected for nucleophilic attack on the quinonoid system (13). The low solubility of the 6-nitro- and 6-acetylamino-amines, makes it difficult to judge their reactivity quantitatively but the latter apparently belongs somewhere high in the order of reactivity.

In the instance of the 1-bromonaphthylamine reaction, sufficient fractions were taken to give a qualitative study of the reaction rate. Fitting the experimental data (crude product weights) to a bimolecular reaction rate curve indicated that one day's standing time was equivalent to about 48 minutes of reflux time. Using this relation, the theoretical curve predicted weights of product which differed from those actually obtained in the various fractions by an average weight of 6 mg. and a maximum weight of 15 mg.

For identification, the absorption spectra of these compounds are shown in Figure 1 and Table II. The spectra were determined on a Cary Automatic Recording Spectrophotometer, Model 11.

EXPERIMENTAL[3]

All melting points are corrected.

Starting materials. Naphthoquinone (E. K. Co.) was purified by recrystallization from diethyl ether (14), m.p. 123.0–124.0°. Commercial *2-aminonaphthalene* (Paragon) was used as obtained, m.p. 110.0–110.5°.

The *nitronaphthylamines* were obtained by the acetylation and nitration of 2-aminonaphthalene and separation of the isomers according to the method of Saunders and Hamilton (15). The 6-isomer melted at 202–204°, the 8-isomer at 100.5–103.5°, and the 1-isomer at 127.0–127.5°.

6-Acetylamino-2-aminoaphthalene. A suspension of 6-nitro-2-aminonaphthalene (18.8 g., 0.100 mole) in acetic acid (100 ml.) was refluxed with acetic anhydride (10.9 g., 0.108 mole)

[3] All analyses were performed by Drs. Weiler and Strauss, 164 Banbury Road, Oxford, England.

for one hour after the initial exothermic reaction had subsided, and allowed to stand for three days at room temperature. Filtration gave 21.3 g. (0.093 mole, 92.5%) of 6-nitro-2-acetylaminonaphthalene m.p. 220.0–222.5° [reported (16) 224°]. Catalytic hydrogenation of this product (10.00 g., 43.5 mmoles) over 5% palladium-charcoal catalyst (0.22 g.) in 95% alcohol (100 ml.) consumed slightly more than the theoretical quantity of hydrogen. Dilu-

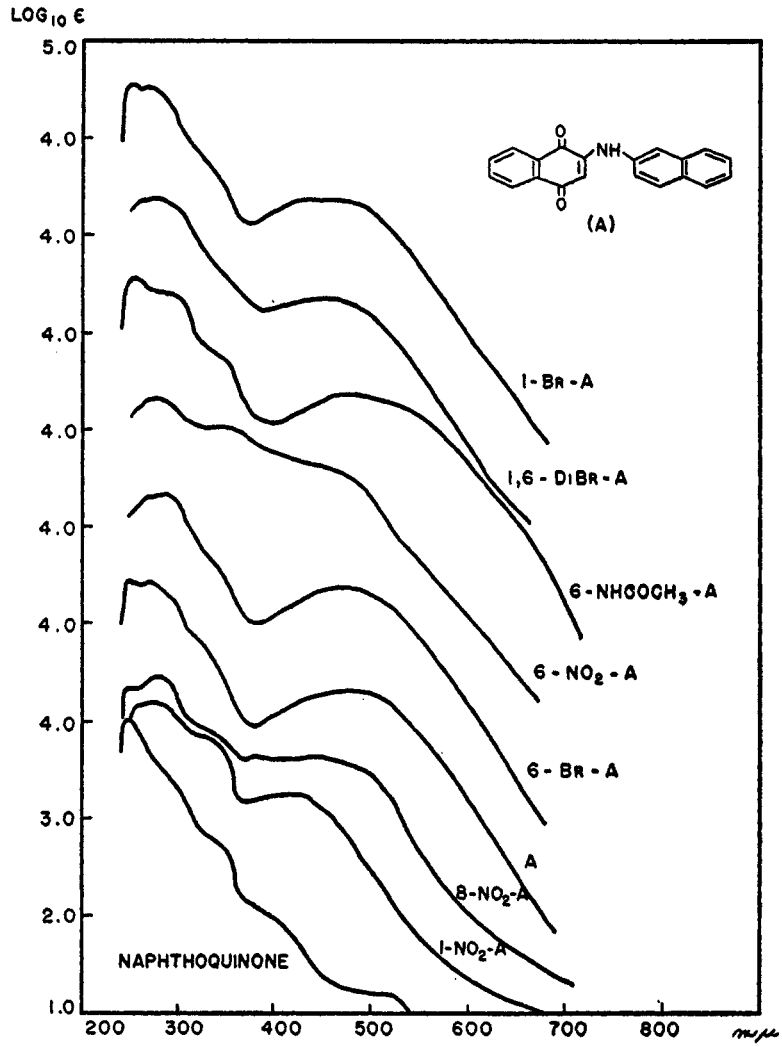


FIGURE 1. ABSORPTION SPECTRA OF NAPHTHYLAMINONAPHTHOQUINONES

tion, heating and filtration gave a dark solid from which the catalyst was removed by dissolution in acetic acid and filtration. Addition of alcohol and water to the acetic acid solution precipitated 0.33 g. of unidentified amorphous high-melting (<260°) solid. The material recovered by addition of strong sodium hydroxide was recrystallized from a mixture of pyridine, alcohol and water, combined with further product obtained by evaporation of the original alcohol filtrate, and recrystallized from alcohol. Vacuum sublimation at 215–225° (2–3 mm.) followed by recrystallization from *n*-propanol gave 0.50 g. (6%) of 6-acetylamino-2-aminonaphthalene, white needles, m.p. 240–244° (dec.).

Anal. Calc'd for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99.
Found: C, 71.34, H, 6.01; N, 14.30.

Bromonaphthylamines. Bromination of 2-acetylaminonaphthalene by the method of Claus and Philipson (17) gave 1,6-dibromo-2-acetylaminonaphthalene (after purification) in 18% yield. Fractional crystallization of the main product indicated that it was a mixture of 1-bromo-2-acetylaminonaphthalene, 1-bromo-2-aminonaphthalene, and 1-bromo-2-aminonaphthalene hydrobromide. The hydrobromide fraction was dissolved in hot alcohol, neutralized with concentrated ammonia, and purified by steam-distillation and recrystallization from dilute alcohol. The resulting 1-bromo-2-aminonaphthalene melted at 60–61.5° [reported (18) 63–64°].

In an adaptation of the method of Claus and Philipson, 52.8 g. (0.330 mole) of bromine was added dropwise to a rapidly stirred solution of 27.75 g. (0.150 mole) of 2-acetylaminonaphthalene and 300 ml. of chloroform in a flask protected by a drying tube. The mixture was allowed to stand for five days with intermittent stirring and refluxing for a total of eight hours during this time.

TABLE II

ABSORPTION MAXIMA OF NAPHTHYLAMINONAPHTHOQUINONES

SUBSTITUENT	MAXIMA					
	λ (mμ)	Log ε	λ (mμ)	Log ε	λ (mμ)	Log ε
None	250	4.452	270	4.425	467	3.310
1-Bromo	250	4.535	270	4.503	440	3.370
6-Bromo	259	4.255	287	4.327	468	3.378
1,6-Dibromo	260	4.376	278	4.388	442	3.364
1-Nitro	260	4.170	281	4.194	410	3.240
6-Nitro	260	4.270	279	4.328	—	—
8-Nitro	280	3.478	380	3.634	446	3.646
6-Acetylamino	255	4.590	289	4.400	465	3.337
1,4-Naphthoquinone (unsubstituted)	247	4.020	—	—	—	—

Filtration gave a crude product which was washed with chloroform and then partially freed of residual chloroform and hydrogen bromide by heating at 90–100° to give 44 g. of nearly white material. Recrystallization from one liter of hot 95% alcohol to which sufficient concentrated ammonia had been added to neutralize residual hydrogen bromide gave 22 g. (0.064 mole, 42.7%) of white 1,6-dibromo-2-acetylaminonaphthalene, m.p. 206–209° [reported (17) 212°].

Deacetylation of 1,6-dibromo-2-acetylaminonaphthalene was accomplished in 94% over-all yield by refluxing 22 hours with concentrated hydrochloric acid in 95% ethanol, recovering the hydrochloride by filtration, and recrystallizing from alcohol and ammonia, m.p. 120–125° [reported (17) 121°].

6-Bromo-2-aminonaphthalene was prepared from the dibromoamine by the method of Franzen and Staüble (18) in 80% yield, m.p. 126–127° [reported (18) 128°].

Aminoquinones. The amine-quinone condensations were carried out in an 8-in. test tube fitted with a reflux condenser and a glass tube (air inlet) extending to the bottom of the test tube. In each reaction a solution of 0.02 g. of cerium (III) chloride in about 15 ml. of absolute alcohol was used as the initial solvent or suspending medium and further solvent was added as necessary to maintain the liquid level. Equimolar quantities of 1,4-naphthoquinone and the desired amine (amounting to a total of 0.76 g. of solids) were dissolved or suspended in the alcohol and alternately refluxed and allowed to stand at room temperature. During the periods of refluxing, air was aspirated through the solution. Suc-

cessive fractions of the product were recovered by filtration of the reaction mixture as desired.

2-(2'-Naphthylamino)-1,4-naphthoquinone. (See Table I.) Recrystallization of fraction 1, twice from benzene and twice from *n*-propanol, gave 0.33 g. (43%) of fine, dark red needles, m.p. 191.5–192.0°.

Anal. Calc'd for $C_{20}H_{13}NO_2$: C, 80.25; H, 4.38; N, 4.68.
Found: C, 80.19; H, 4.38; N, 4.46.

In a second run using 95% alcohol the crude yield was 0.47 g. (m.p. 180–190°) in the first fraction and 0.16 g. (m.p. 175–183°) for the second.

2-(1'-Bromo-2'-naphthylamino)-1,4-naphthoquinone. (See Table I.) Repeated recrystallization of fractions 1–5 from *n*-propanol gave 0.27 g. (35%) of red-orange needles, m.p. 228.5–229.5°.

Anal. Calc'd for $C_{20}H_{12}BrNO_2$: C, 63.51; H, 3.20; Br, 21.13; N, 3.70.
Found: C, 63.05; H, 3.26; Br, 21.05; N, 3.99.

2-(6'-Bromo-2'-naphthylamino)-1,4-naphthoquinone. (See Table I.) Fractions 1–3 were recrystallized from *n*-propanol to yield 0.49 g. (65%) of dark red needles, m.p. 228.5–229.5°.

Anal. Calc'd for $C_{20}H_{12}BrNO_2$: C, 63.51; H, 3.20; Br, 21.13; N, 3.70.
Found: C, 63.15; H, 3.22; Br, 20.90; N, 3.90.

2-(1',6'-Dibromo-2'-naphthylamino)-1,4-naphthoquinone. (See Table I.) Sufficient sulfuric acid (in alcohol) was added, after removing the first fraction, to neutralize 19% of the original amine present. Fractions 1–4 were recrystallized from benzene to yield fluffy orange-red needles (0.31 g., 41%), m.p. 257–258°.

Anal. Calc'd for $C_{20}H_{11}Br_2NO_2$: C, 52.58; H, 2.43; Br, 34.96; N, 3.06.
Found: C, 52.58; H, 2.51; Br, 34.80; N, 3.18.

2-(1'-Nitro-2'-naphthylamino)-1,4-naphthoquinone. Refluxing the solution of reactants for 2.5 hours in the usual manner and standing for 24 hours gave no precipitate. Enough sulfuric acid in alcohol was added to neutralize about 15% of the amine. After a further total of ten hours refluxing over the course of 19 days 0.15 g. of partially infusible solid was recovered. Leaching with benzene, evaporation of the resulting solution to dryness, and repeated recrystallization of the residue from *n*-butanol gave 37 mg. of brownish orange needles, m.p. 212.5–214.0° (insufficient material was available for satisfactory recrystallization).

Anal. Calc'd for $C_{20}H_{12}N_2O_4$: C, 69.76; H, 3.51; N, 8.14.
Found: C, 70.87; H, 3.66; N, 7.63.

2-(6'-Nitro-2'-naphthylamino)-1,4-naphthoquinone. Although the amine was largely insoluble in alcohol, the reaction mixture was filtered after refluxing 2 hours and allowing to stand 24 hours. The resulting solid, 0.57 g., m.p. 115–185°, was recrystallized from *n*-propanol to give 0.24 g. of brown crystals, m.p. 195–201°, mixture with starting amine 195–201°. Refluxing the original filtrate for 4.5 hours over the course of 11 days and filtering gave 0.06 g. of crystals, m.p. 290–305°. Recrystallization from pyridine gave 22 mg. (3%) of bright red crystals, m.p. 303.5–304.5°.

Anal. Calc'd for $C_{20}H_{12}N_2O_4$: C, 69.76; H, 3.51; N, 8.14.
Found: C, 69.42; H, 3.73; N, 8.21.

2-(8'-Nitro-2'-naphthyalmino)-1,4-naphthoquinone. (See Table I.) Recrystallization of fraction 1 from *n*-propanol gave 0.17 g. of crystals m.p. 276–282°, which were combined with fractions 2 and 3 and recrystallized twice from pyridine to give 0.11 g. (15%) of dark purple-red needles, m.p. 283.5–284.5°.

Anal. Calc'd for $C_{20}H_{12}N_2O_4$: C, 69.76; H, 3.51; N, 8.14.
Found: C, 69.75; H, 3.34; N, 8.17.

2-(6'-Acetylamino-2'-naphthylamino)-1,4-naphthoquinone. The reaction slurry was refluxed for eight hours over the course of seven days and filtered to give 0.60 g. of crystals, m.p. 280–290°. Repeated recrystallization from pyridine gave 0.33 g. (43%) of purplish-black needles, m.p. 294.5–295.5°.

Anal. Calc'd for $C_{22}H_{16}N_2O_3$: C, 74.14; H, 4.53; N, 7.86.
Found: C, 74.28; H, 4.64; N, 8.27.

SUMMARY

A series of 2-(substituted-2′-naphthylamino)-1,4-naphthoquinones were prepared for biological testing. The one-step addition of the substituted 2-naphthylamine to 1,4-naphthoquinone in the presence of cerium (III) chloride and air gave the following new naphthylaminoquinones: 2-(2′-naphthylamino- , 2-(1′-bromo- , 2-(6′bromo- , 2-(6′-acetylamino- , 2-(1′,6′-dibromo- , 2-(6′-nitro- , 2-(8-nitro- , and 2-(1′-nitro-2-naphthylamino)-1,4-naphthoquinone.

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REFERENCES

(1) FIESER AND FIESER, *Organic Chemistry*, D. C. Heath and Co., Boston, Mass., 1944, p. 746 ff.
(2) SJÖGREN, *The Svedburg*, edited by A. Tiselius, Almqvist and Wiksells, Uppsala, Sweden, 1944, p. 547.
(3) SJÖGREN, *Nature*, **150**, 431 (1942).
(4) SJÖGREN AND BERLIN, *Svensk Kem. Tid.*, **54**, 200 (1942); [*Chem. Abstr.*, **38**, 3629 (1944)].
(5) LLOYD AND MIDDLEBROOK, *Am. Rev. Tuberc.*, **49**, 539 (1944).
(6) CALANDRA AND ADAMS, *J. Am. Chem. Soc.*, **72**, 4804 (1950).
(7) BUU-HOÏ, *Bull. soc. chim. France*, **11**, 578 (1944).
(8) HOFMANN, *Jahresber. Fortschr. Chem.*, 415 (1863).
(9) HAUSCHKA, *J. prakt. Chem.*, [2] **90**, 447 (1914).
(10) GROSSMANN, *J. prakt. Chem.*, [2] **92**, 370 (1915).
(11) FIESER, *J. Am. Chem. Soc.*, **57**, 491 (1935).
(12) LUCIUS AND BRÜNING, German Patent 262,180 (1913).
(13) HAMMETT, *Physical Organic Chemistry*, McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 184, 346.
(14) FIESER, in *Org. Syntheses*, Coll. Vol. I, 2nd edition, 343 (1941).
(15) SAUNDERS AND HAMILTON, *J. Am. Chem. Soc.*, **54**, 636 (1932).
(16) VESELY AND JAKES, *Bull. soc. chim.*, **33**, 942 (1923).
(17) CLAUS AND PHILIPSON, *J. prakt. Chem.*, [2] **43**, 47 (1891).
(18) FRANZEN AND STAÜBLE, *J. prakt. Chem.*, [2] **101**, 58 (1921).