0.429 mol) was added to a solution of 20.0 g (0.107 mol) of 2-(methylthio)ethyl methanethiolsulfonate[12] in 200 ml of absolute ethyl ether with stirring. The reaction mixture was allowed to stand at room temperature for 15 hr and was thereafter filtered to remove the by-product piperidinium methanesulfinate. The ether was removed from the filtrate by evaporation *in vacuo*, leaving a residue of crude product and excess piperidine. The residue was stirred with water and extracted with methylene chloride. The extract was dried over anhydrous magnesium sulfate; and, after removal of the solvent by evaporation, the residue was fractionated, giving the pure product as 16.5 g (80%) of colorless liquid: bp 76–82° (0.6 mm); $n^{25}D$ 1.5345.

Anal. Calcd for $C_8H_{17}NS_2$: C, 50.21; H, 8.96; N, 7.32. Found: C, 50.4; H, 8.77; N, 7.54.

2-(Methylthio)ethyl 1-Piperidinecarbotrithioate (IIIf).—The procedure was the same as that used for the preparation of IIIc, using 12.7 g (0.0665 mol) of 1-[2-(methylthio)ethylthio]piperidine and 100 ml of carbon disulfide. The crude product was obtained as 13.7 g (77%) of yellow crystals, mp 42–43.5°. Recrystallization from 2-propanol gave the pure substance as colorless crystals: mp 44°; nmr ($CDCl_3$) δ 1.73 (br s, 6, $NCH_2CH_2CH_2CH_2CH_2$), 2.13 (s, 3, SCH_3), 2.94 (m, 4, SCH_2CH_2S), and 4.14 ppm (s, 4, CH_2NCH_2).

Anal. Calcd for $C_9H_{17}NS_4$: C, 40.41; H, 6.41; N, 5.24. Found: C, 40.45; H, 6.37; N, 5.23.

N-[2-(Methylthio)ethylthio]dimethylamine.—An excess of anhydrous dimethylamine gas was passed through a solution of 37.2 g (0.200 mol) of 2-(methylthio)ethyl methanethiolsulfonate[12] in 300 ml of absolute ethyl ether at room temperature with stirring over a period of 30 min. The precipitated by-product, dimethylammonium methanesulfinate, was removed by filtration, and the ether filtrate was washed with water and dried over anhydrous magnesium sulfate. The ether was removed by evaporation *in vacuo*, and the residual oil was fractionated to give the pure product as 24.8 g (82%) of colorless oil: bp 41° (0.6 mm); $n^{25}D$ 1.5148.

Anal. Calcd for $C_5H_{13}NS_2$: C, 39.69; H, 8.66; N, 9.26. Found: C, 39.8; H, 8.48; N, 9.00.

2-(Methylthio)ethyl Dimethylaminecarbotrithioate (IIIg).—The procedure was the same as that for IIIc, using 15.1 g (0.100 mol) of N-[2-(methylthio)ethylthio]dimethylamine and 100 ml of carbon disulfide. The crystalline crude product was recrystallized from methanol to give 20.2 g (89%) of the pure substance as colorless needles: mp 35.5–36.5°; nmr ($CDCl_3$) δ 2.13 (s, 3, SCH_3), 2.93 (m, 4, CH_2CH_2), and 3.53 ppm [s, 6, $N(CH_3)_2$].

Anal. Calcd for $C_6H_{13}NS_4$: C, 31.69; H, 5.76; N, 6.16. Found: C, 31.7; H, 6.00; N, 5.93.

Registry No.—Carbon disulfide, 75-150; 1-[2-(methylthio)ethylthio]piperidine, 22158-14-1; N-[2-(methylthio)ethylthio]dimethylamine, 22158-16-3; IIIa, 22158-09-4; IIIb, 22158-10-7; IIIc, 22158-11-8; IIId, 22158-12-9; IIIe, 22158-13-0; IIIf, 22158,15-2; IIIg, 22158-17-4.

Acknowledgment.—The authors wish to express their appreciation for the technical assistance of Mrs. Betty H. Tarnowski.

Synthesis of 2-Alkylamino-3-hydroxy-1,4-naphthoquinones[1]

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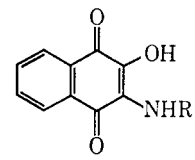
Although numerous 1,4-naphthoquinones have been synthesized and investigated, 2-alkylamino-3-hydroxy-1,4-naphthoquinones (I) have not been reported in the literature. The importance of compounds of type I can be exemplified by the interesting biological activities associated with many 3-alkyl- and 3-alkenyl-substituted derivatives of lawsone (2-hydroxy-1,4-naphthoquinone)[2] and arylamino-1,4-naphthoquinones.[3] Further need for a study of compounds of this type is illustrated by the observation that the *ortho*-amino quinoid unit is present in many antitumor antibiotics such as actinomycins, mitomycin C, porfiromycin, and streptonigrin.[4]



I

In connection with a study of the Mannich reaction of lawsone, the synthesis of 2-alkylamino-3-hydroxy-1,4-naphthoquinones was attempted by Dalgliesh[5] some 20 years ago. The methods involved treatment of lawsone with an amine, the reaction of amines with 2,3-dichloro-1,4-naphthoquinone followed by hydrolysis, and the rearrangement of aminonaphthoquinone oxide. None of these procedures proved to be successful. Certain 2-arylamino-3-hydroxy-1,4-naphthoquinones have been obtained by treatment of naphthoquinone oxide[2a] with aromatic amines[6] or by heating a mixture of aniline and 2-chloro-3-hydroxy-1,4-naphthoquinone.[7] When these reaction conditions were used in this laboratory for the preparation of the corresponding aliphatic amino compounds, the desired product could not be isolated. In addition, the product could not be prepared by the catalytic reduction of a mixture of the nitro compound II and the appropriate aldehyde.[8]

Compounds of type I were successfully prepared by the following general method. 2-Hydroxy-3-nitro-1,4-naphthoquinone[9] (II), prepared by the treatment of 2,3-dichloro-1,4-naphthoquinone with sodium nitrite,[10] was hydrogenated in glacial acetic acid in the presence of Adam's catalyst. To the intermediate 2-amino-1,3,4-trihydroxynaphthalene (III), *in situ*, was added the appropriate acyl chloride. The resulting reaction mixture was oxidized in air to yield the 2-acylamido-3-hydroxy-1,4-naphthoquinone (IV), which was readily reduced to the desired compound I with lithium aluminum hydride.

(1) This investigation was supported by the Cancer Chemotherapy National Service Center, National Cancer Institute, of the National Institutes of Health, U. S. Public Health Service, Contract No. PH-43-65-94.

(2) See, *e.g.*, (a) L. F. Fieser, *et al.*, *J. Amer. Chem. Soc.*, **70**, 3151, 3156, 3165, 3174, 3212, 3215, 3228, 3232, 3237 (1948); (b) M. T. Leffler and R. J. Hathaway, *ibid.*, **70**, 3222 (1948); (c) H. E. Zaugg, R. T. Rapala, and M. T. Leffler, *ibid.*, **70**, 3224 (1948); (d) P. Truitt, F. Mahon, O. Platas, R. L. Hall, and T. E. Eris, *J. Org. Chem.*, **25**, 962 (1960); (e) D. A. Berberian and R. G. Slighter, Jr., *J. Parasitol.*, **54**, 999 (1968); (f) D. A. Berberian, R. G. Slighter, Jr., and H. W. Freele, *ibid.*, **54**, 1181 (1968); (g) K. V. Rao, T. J. McBride, and J. J. Oleson, *Cancer Res.*, **28**, 1952 (1968).

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(5) C. E. Dalgliesh, *ibid.*, **71**, 1697 (1949).

(6) I. F. Vladimirtsev, *Zh. Obshch. Khim*, **30**, 2670 (1960).

(7) P. Truitt, J. E. Cooper, III, and F. M. Wood, Jr., *J. Amer. Chem. Soc.*, **79**, 5708 (1957).

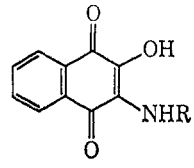
(8) R. T. Major, *ibid.*, **53**, 1901 (1931).

(9) T. Diehl and V. Merz, *Ber.*, **11**, 1314 (1878).

(10) (a) F. Kehrmann and O. Weichardt, *J. Prakt. Chem.*, [2] **40**, 179 (1889); (b) A. Inoue, N. Kuroki, and K. Konishi, *Yûki Gôsei Kagaku Kyôkai Shi*, **17**, 714 (1959); *Chem. Abstr.*, **54**, 4504e (1960).

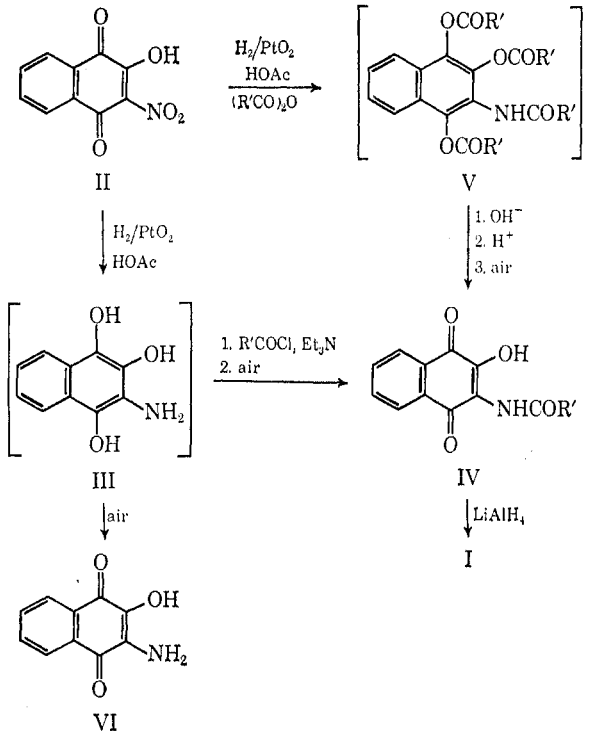
TABLE I

2-ALKYLAMINO-3-HYDROXY-1,4-NAPHTHOQUINONES



Registry no.	R	Yield, %	Mp, °C	Formula	Anal., % Calcd C	Calcd H	Calcd N	Found C	Found H	Found N	Uv absorption pH 1 λmax, mμ	pH 1 ε × 10⁻³	pH 11 λmax, mμ	pH 11 ε × 10⁻³	Ethanol λmax, mμ	Ethanol ε × 10⁻³
22158-41-4	H	53	242–245 dec	$C_{10}H_7NO_3$	63.49	3.70	7.40	63.68	3.79	7.35	248	10.0	236	15.9	230	16.2
											280	23.0	294	22.2	281	24.7
22158-42-5	C_2H_5	25	127–128	$C_{12}H_{11}NO_3$	66.35	5.10	6.45	66.41	5.07	6.38	245	15.0	236	13.0	236	15.4
											250	17.8	291	19.1	287	21.0
											266	13.5				
											277	13.7				
22158-43-6	$CH_3(CH_2)_6$	61	95–97	$C_{17}H_{21}NO_3$	71.06	7.37	4.88	71.08	7.45	3.95	244	14.4	239	13.5	236	17.0
											250	16.4	293	19.3	288	22.4
											276	13.5				
21158-44-7	$CH_3(CH_2)_{11}$	21	86–87	$C_{22}H_{31}NO_3$	73.91	8.74	3.92	73.97	8.64	3.89	240	14.6	240	13.2	230	16.1
											295 (sh)	17.5	295 (sh)	11.1	286	18.6
											307	18.2			300 (sh)	16.4
22158-45-8	$CH_3(CH_2)_{12}$	61	89	$C_{23}H_{33}NO_3$	74.36	8.95	3.77	74.59	9.20	3.98	243	15.3	242	13.8	233	17.5
											297 (sh)	20.2	295 (sh)	13.4	288	23.0
											308	21.6			300 (sh)	20.4

For the preparation of the short-chain ethylamino derivative wherein the acid anhydride is readily available, the anhydride can be added to the nitronaphthoquinone–acetic acid mixture prior to the catalytic hydrogenation. The reduced acetylated intermediate V was hydrolyzed and oxidized to yield IV, which was then reduced to give I (R = C_2H_5).



II V III IV I VI

2-Amino-3-hydroxyl-1,4-naphthoquinone (VI), the parent compound of I, has been reported in the literature, albeit with different melting points. Diehl and Merz[9] prepared VI by chemical reduction of II and reported that the product turned black at 100°, whereas the product obtained by Carrara and Bonacci[11] by a similar procedure melted with decomposition at 130–140°. Compound VI has now been prepared by both catalytic and chemical reduction of II, yielding identical products melting at 242–245° with decomposition. Elemental analysis and ultraviolet absorption maxima of compound VI are listed in Table I along with those of the alkylamino analogs. Molecular weight, as determined by mass-spectrum analysis, was found to correspond with the calculated value for compound VI.

Experimental Section[12]

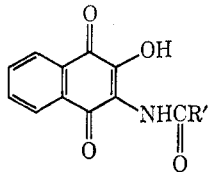
General Preparation of 2-Acylamido-3-hydroxy-1,4-naphthoquinones (IV). Procedure A.—A Parr hydrogenation flask was charged with 10.0 g (0.046 mol) of 2-hydroxy-3-nitro-1,4-naphthoquinone (II), 100 ml of glacial acetic acid, and 0.1 g of platinum oxide and subjected to hydrogenation at 4.2 kg/cm² for 2 hr. During this interval, *ca.* 4 equiv of hydrogen was taken up. The course of the reduction can be readily followed by the pronounced color changes. The initial pale yellow color of II readily changes to purple, which in turn fades completely to give a colorless solution as the ring carbonyls are reduced. The flask was removed from the hydrogenator and chilled under a slow stream of nitrogen, care being taken to exclude air in all operations. Then 6 ml of triethylamine and 0.046 mol of the appropriate acid chloride were added, in that order, to the flask with occasional shaking, at such a rate as to keep the temperature of the mixture at 5–10°. The reaction mixture was maintained at ice-bath temperature for 2 hr, and allowed to stand at room temperature overnight under nitrogen. It was then filtered, and the filtrate, which gradually changed from a pale yellow to a deep red as the oxidation of the intermediate dihydroxy compound progressed, was concentrated in a hood by passing a stream of air over the surface. The resulting residue was recrystallized from methanol [for R′ = $CH_3(CH_2)_5$, acetone and water] to give the desired acylamido compound IV as orange platelets (see Table II).

(11) G. Carrara and G. Bonacci, *Chim. Ind.* (Milan), **26**, 75 (1944).

(12) All melting points (corrected) were taken on a Thomas–Hoover melting point apparatus. The ultraviolet absorption spectra were determined with a Beckman DK-2 spectrophotometer.

TABLE II

2-ACYLAMIDO-3-HYDROXY-1,4-NAPHTHOQUINONES



Registry no.	R′	Yield, %	Mp, °C	Formula	Anal., % Calcd C	Calcd H	Calcd N	Found C	Found H	Found N	Uv absorption: pH 1 λmax, mμ	pH 1 ε × 10⁻³	pH 11 λmax, mμ	pH 11 ε × 10⁻³	Ethanol λmax, mμ	Ethanol ε × 10⁻³
22157-98-8	CH_3	72[a]	220–223	$C_{12}H_9NO_4$	62.34	3.92	6.06	62.10	3.67	5.84	250 280	17.1 12.5	267	20.8	270	20.6
22188-53-0	$CH_3(CH_2)_5$	47[b]	133–134	$C_{17}H_{19}NO_4$	67.76	6.36	4.65	67.57	6.35	4.65	251 283	17.8 12.3	232 269	14.2 24.4	273	22.6
22157-99-9	$CH_3(CH_2)_{10}$	42[b]	127–128	$C_{22}H_{29}NO_4$	71.13	7.87	3.77	71.32	7.86	3.64	304	20.4	268	23.4	270	21.9
22158-00-5	$CH_3(CH_2)_{11}$	51[b]	124–125	$C_{23}H_{31}NO_4$	71.66	8.11	3.63	71.72	8.33	3.59	304	18.8	269	18.8	270	19.3

[a] Prepared by procedure B (see Experimental Section). [b] Prepared by procedure A (see Experimental Section).

Procedure B.—A mixture of 10 g of II, 100 ml of glacial acetic acid, 25 ml of acetic anhydride, and 0.1 g of platinum oxide was hydrogenated at 4.2 kg/cm². After 2 hr, *ca.* 4 equiv of hydrogen were absorbed. The reaction mixture was then filtered and the filtrate was evaporated *in vacuo* at 30° to yield an off-white residue. This was dissolved in 100 ml of 2 *N* potassium hydroxide at room temperature and the red-brown solution was filtered after being stirred for 2 hr. Acidification of the filtrate with dilute hydrochloric acid yielded the desired product, which was isolated by filtration. The product IV (R′ = CH_3) was usually of analytical quality and, in any event, was generally suitable for use in the following preparations without further purification.

General Preparation of 2-Alkylamino-3-hydroxy-1,4-naphthoquinones (I).—The acylamido compound (*ca.* 0.015 mol), dissolved in 125 ml of dry tetrahydrofuran, was added, at room temperature during 30 min, with stirring and under dry nitrogen, to a large excess (*ca.* 0.1 mol) of lithium aluminum hydride in 200 ml of dry tetrahydrofuran. The gray-green reaction mixture was then refluxed with stirring for 10 hr. The resulting mixture was chilled to about 5° and slowly hydrolyzed by the dropwise addition of 15 ml of water followed by 100 ml of 10% sulfuric acid. The bulk of the tetrahydrofuran was evaporated and the resulting intermediate was oxidized by passing a stream of air over the stirred solution, which rapidly turned purple. About 100 ml of water was added and the remaining tetrahydrofuran was removed *in vacuo*. The resulting solid and aqueous phases were extracted with ether. Better yields may be obtained by continuous extraction of the aqueous phase. The ether extracts were combined, dried over anhydrous sodium sulfate, filtered, and evaporated to dryness. Products of analytical purity are obtained by recrystallization from 95% ethanol.

2-Hydroxy-3-amino-1,4-naphthoquinone (VI). Procedure A.—A solution of 10.95 g (0.05 mol) of 2-hydroxy-3-nitro-1,4-naphthoquinone (II) in 200 ml of methanol was subjected to hydrogenation in a Parr shaker at 4.2 kg/cm² using platinum oxide as catalyst. *Ca.* 4 equiv of hydrogen were taken up within 30 min. (Color changes are indicated in procedure A of the general preparation for compounds IV.) On exposure to air, the colorless solution immediately turned to purple as the intermediate was oxidized. The reaction mixture was warmed gently on the steam bath and filtered. The filtrate was concentrated to *ca.* one-half volume by evaporation under a stream of air while warming on a steam bath. After the filtrate had stood overnight at room temperature, dark red crystals were deposited. The crystals were collected by filtration and dried at 25° (0.1 mm) for 18 hr to yield 5.0 g (53%) of product, mp 242–245° dec.

Procedure B.—A solution of 10 g of sodium hydrosulfite in 100 ml of water was added to 3 g of 2-hydroxy-3-nitro-1,4-naphthoquinone (II) in 50 ml of ethanol at 50°. The reaction mixture was warmed for 15 min on the steam bath, whereupon some crystals began to separate. When the mixture was cooled and exposed to air, additional product separated. The product was collected by filtration and dried at reduced pressure to give 2.0 g (77%): mp 242–244° dec (lit. mp 130–140° dec;[11] darkened at 100° [9]); mol wt 189 (mass spectrum, 70 eV).

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The Behavior of Dithio Acids toward Nitro Derivatives of Chlorobenzene[1]

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The crystalline thio ethers which are formed by the reaction of 2,4-dinitrochlorobenzene with alkali mercaptide have been used for identification of the latter.[3]

The present work was attempted to investigate the reaction of *gem*-dithiols with nitro derivatives of chlorobenzene. The dithiols and the nitro derivatives of chlorobenzene used here were di(sodiomercapto)methylene malononitrile (Ia), di(sodiomercapto)methylene methyl cyanoacetate (Ib), di(sodiomercapto)methylene ethyl cyanoacetate (Ic), di(sodiomercapto)methylene cyanoacetamide (Id), *o*- and *p*-nitrochlorobenzene, 2,4-dinitrochlorobenzene, and picryl chloride.

When 2,4-dinitrochlorobenzene (2,4-DNCB) reacted with Ia, Ib, and Ic, 2-dicyanomethylene-5-nitro-1,3-benzodithiole (IIa), 2-acetocarbonylcyanomethylene-5-nitro-1,3-benzodithiole (IIb), and 2-carbethoxycyano-5-nitro-1,3-benzodithiole (IIc), respectively, were obtained. The reaction of picryl chloride (2,4,6-TNCB) with Ia, Ib, and Ic gave 2-dicyanomethylene-4,6-dinitro-1,3-benzodithiole (IIIa), 2-methoxycarbonylcyanomethylene-4,6-dinitro-1,3-benzodithiole (IIIb),

(1) A part of this paper was read at the 22nd Annual Meeting of the Chemical Society of Japan, Tokyo, April 1969.

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