SYNTHESIS OF SOME NOVEL NAPHTHOQUINONE FUSED SELENAZOLES AND 2-AMIMNO-3-ALKYLSELENO-1,4-NAPHTHO-QUINONES

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In honor of the 65th anniversary of Professor Alan R. Katritzky

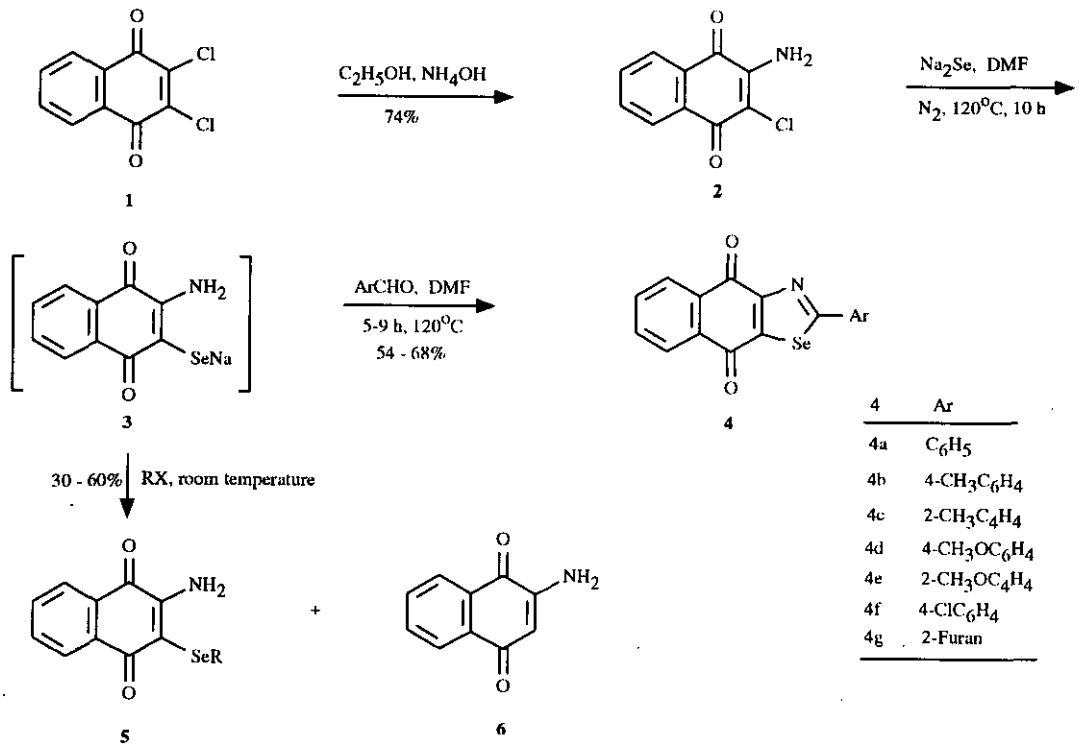
Abstract - A variety of 2-aryl-4,9-dioxonaphtho[2,3-*d*]selenazoles (**4**) are prepared from reactions of appropriate aromatic aldehydes and 2-amino-3-seleno-1,4-naphthoquinone sodium salt (**3**), which is prepared from 2-amino-3-chloronaphthoquinone *(2)*, sodium and selenium powder without isolation. The intermediate (**3**) reacts with a range of alkyl halides to give 2-amino-3-alkyl-seleno-1,4-naphthoquinones (**5**).

The selenazole ring was reported for the first time in 1889 by Hofmann.[1] Monocyclic selenazoles are obtained almost exclusively by the reaction of selenoamides with α-halocarbonyl compounds.[2] Although there are two reviews available covering the field of selenazole chemistry,[3,4] only a few works related to this class of compounds have been reported. Moreover, condensed selenazoles are far less exploited compared with the corresponding thiazoles.[5] The most general synthesis of benzoselenazoles involves the reaction of the zinc salt of *o*-aminobenzeneselenolate with acid chlorides, in this way are obtained 2-alkyl-, 2-aryl- and 2-hetarylbenzoselenazoles.[6-8] Naphthoselenazole ring systems are known only in rare cases: 2-acetamido-naphtho[1,2-*d*]selenazole is prepared by the cyclization of 4-phenyl-2-amino-5-carboxyethylselenazole with acetic anhydride;[9] and 2-aminonaphtho[1,2-*d*]selenazole is obtained from 1-cyanoseleno-2-aminonaphthalene.[10] So far, no general synthesis of naphthoselenazoles has been reported. We now describe the synthesis of a novel class of naphthoquinone condensed selenazoles, 2-aryl-4,9-dioxonaphtho[2,3-*d*]selenazoles.

2,3-Dihalo-1,4-naphthoquinones undergo nucleophilic substitutions with a variety of amines, thiols and alcohols to give 2,3-disubstituted naphthoquinones.[11-14] We have recently reported the preparation of 2,3-bis(alkyl-

seleno)-1,4-naphthoquinones by reactions of 2,3-dichloro-1,4-naphthoquinone and alkyl selenoates.[15] The infrared absorbing dyes of phenothiazinequinone and phenoselenazinequinone type have been prepared by the ring-closure reaction of halogenoquinones with potassium 2-aminobenzenethiolate or zinc 2-aminobenzeneselenolate.[16] Many naphthoquinone-fused thiazoles have previously been prepared from the reactions of 2-mercapto-3-amino-1,4-naphthoquinone sodium salt (prepared *in situ* from 2-amino-3-chloro-1,4-naphthoquinone and sodium sulfide) and appropriate aldehydes.[17,18] We have now investigated the analogous reaction with 2-amino-3-seleno-1,4-naphthoquinone sodium salt to prepare naphthoquinone-fused selenazoles.

Scheme 1



4	Ar
4a	C_6H_5
4b	4-$CH_3C_6H_4$
4c	2-$CH_3C_4H_4$
4d	4-$CH_3OC_6H_4$
4e	2-$CH_3OC_4H_4$
4f	4-ClC_6H_4
4g	2-Furan

2,3-Dichloro-1,4-naphthoquinone (**1**) was readily converted into 2-amino-3-chloro-1,4-naphthoquinone (**2**) by reaction with ammonium hydroxide as described previously.[19] Heating compound (**2**) under nitrogen with sodium selenide (prepared *in situ* from selenium powder and sodium metal in THF) in DMF gave a deep green solution, which was evidently the sodium salt of 2-seleno-3-amino-1,4-naphthoquinone (**3**). This deep green solution, without isolation, reacted further with an appropriate aromatic aldehyde in DMF at 120 °C to afford the expected products, 2-aryl-4,9-dioxonaphtho[2,3-*d*]selenazoles (**4**) as shown in Scheme 1. Presumably, the selenazoline intermediate formed initially was spontaneously oxidized to selenazole during the reaction and

isolation, similar to the preparation of thiazoles from 2-amino-3-chloro-1,4-naphthoquinone and an aldehyde as previously reported.[17] However, all attempts to isolate the intermediate 2-amino-3-hydroseleno-1,4-naphthaquinone failed. Aldehydes employed included benzaldehyde, 4-tolualdehyde, 2-tolualdehyde, 4-anisaldehyde, 2-anisaldehyde, 4-chlorobenzaldehyde and 2-furaldehyde, and all gave naphthoquinone-fused selenazoles (**4a-4g**) in 54-68% yields. These novel condensed selenazoles contain the naphthoquinone chromophore, therefore they are colored (yellow or red) in the solid state.

Table 1. Preparations of selenazoles (4a - 4g) and 2-amino-3-alkylseleno-1,4-naphthoquinones (5a -5f)

Comp.	Ar or R	R X	time (h)	Yield (%)	mp (°C)	Formula	Calcd			Found		
							C	H	N	C	H	N
4a	Ph			66	244-245	$C_{17}H_9NO_2Se$	60.37	2.68	4.14	60.50	2.60	3.84
4b	4-$CH_3C_6H_4$			68	246-247	$C_{18}H_{11}NO_2Se$	61.38	3.15	3.98	61.29	3.08	3.61
4c	2-$CH_3C_6H_4$			60	235-237	$C_{18}H_{11}NO_2Se$	61.38	3.15	3.98	61.05	2.97	3.64
4d	4-$CH_3OC_6H_4$			61	268-270	$C_{18}H_{11}NO_3Se$	58.71	3.01	3.80	58.60	2.88	3.68
4e	2-$CH_3OC_6H_4$			54	285-288	$C_{18}H_{11}NO_3Se$	58.71	3.01	3.80	58.73	2.85	3.80
4f	4-ClC_6H_4			62	314-316	$C_{17}H_8ClNO_2Se$	54.79	2.16	3.76	54.90	1.96	3.54
4g	2-furan			58	278-280	$C_{15}H_7NO_3Se$	54.90	2.15	4.27	54.74	1.95	3.86
5a	n-C_3H_7	n-C_3H_7Br	0.5	39	85-86	$C_{13}H_{13}NO_2Se$	53.06	4.42	4.76	52.80	4.26	4.78
5a	n-C_3H_7	n-C_3H_7I	0.15	40	85-86	$C_{13}H_{13}NO_2Se$	53.06	4.42	4.76	53.20	4.25	4.78
5b	n-C_4H_9	n-C_4H_9Cl	5.0	36	82-83	$C_{14}H_{15}NO_2Se$	54.54	4.87	4.54	54.20	4.69	4.42
5c	s-C_4H_9	s-C_4H_9Br	1.0	30	128-130	$C_{14}H_{15}NO_2Se$	54.54	4.87	4.54	54.20	4.88	4.47
5c	s-C_4H_9	s- C_4H_9I	0.5	34	128-130	$C_{14}H_{15}NO_2Se$	54.54	4.87	4.54	54.60	4.91	4.49
5d	$PhCH_2$	Ph_2CH_2Cl	0.1	52	141-143	$C_{17}H_{13}NO_2Se$	59.64	3.80	4.09	59.63	3.73	3.96
5e	allyl	CH_2=$CHCH_2Cl$	0.1	47	91-92	$C_{13}H_{11}NO_2Se$	53.42	3.76	4.79	53.28	3.62	4.83
5f	$CH_3O_2CCH_2$	CH_3OCCH_2Cl	0.1	61	123-124	$C_{13}H_{11}NO_4Se$	48.40	3.40	4.30	48.30	3.20	4.55

The ir, ^1H and ^{13}C-nmr spectra and elemental analyses of 2-aryl-4,9-dioxonaphtho[2,3-*d*]selenazoles (**4a**) to (**4g**) agreed with the assigned structures. Two different carbonyl signals appeared at around 180 and 178 ppm in the ^{13}C-nmr spectra. Compounds (**4d**, **4f** and **4g**) were only sparingly soluble in either $CDCl_3$ or DMSO-d_6 so that their ^{13}C nmr spectra could not be obtained. In the ir spectra, the two absorption maxima of the quinone carbonyl groups occurred at 1680-1690 and 1660-1670 cm^{-1}, respectively. In their ^1H-nmr spectra, two doublet-doublets appeared at 8.3 and 8.2 ppm were assigned as the H-5 and H-8 protons of the naphthoquinone

ring, two other protons were observed as multiplets at 7.8 - 7.7 ppm.

Alkaneselenols and aromatic selenols are good nucleophiles, they react with alkyl halides to give the corresponding symmetrical or unsymmetrical selenides.[4] We now describe the preparation of a novel class of selenides containing the 1,4-naphthoquinone structure. The solution of the sodium salt of 2-amino-3-seleno-1,4-naphthoquinone (**3**) in DMF reacted *in situ* with various alkyl halides under nitrogen at room temperature to give 2-amino-3-alkylseleno-1,4-naphthoquinones (**5a - 5f**) as shown in Scheme 1. Alkyl halides employed included n-propyl bromide and iodide, n-butyl chloride, sec-butyl bromide and iodide, benzyl chloride, allyl chloride and methyl chloroacetate. The yields of the desired products range 30-61% (Table 1). Generally, the active alkyl halides (e.g. benzyl and allyl halides) afforded high yields, and relatively low yields of the compounds (**5**) were obtained from secondary alkyl halides. This result is consistent with the SN2 mechanism. Besides 2-amino-3-alkylseleno-1,4-naphthoquinones, a by-product, 2-amino-1,4-naphthoquinone (**6**), was isolated in all cases, and when a tertiary alkyl halide was used as an electrophile, only 2-amino-1,4-naphthoquinone was formed and no desired product was obtained. Compound (**6**) was identified by the elemental analysis, by its ^{1}H nmr spectrum and by comparison with authentic specimen (mp, 205-207 ^{o}C; lit.,[20] 206 ^{o}C). Obviously, elimination reaction, in which 2-amino-3-seleno-1,4-naphthoquinone function as a base, competes with the nucleophilic substitution, and when the tertiary alkyl halide was used, elimination was the exclusive process. 2-Amino-1,4-naphthoquinone is thus formed through the oxidation of the elimination product 2-amino-3-hydroseleno-1,4-naphthoquinone. Selenols are generally sensitive to air and often undergo the oxidative decomposition to selenium powder and alkanes.[4]

All 2-amino-3-alkylseleno-1,4-naphthoquinones (**5a - 5f**) are new compounds, their structures were readily characterized by their elemental analyses (Table 1) and by their ^{1}H and ^{13}C nmr spectra. Two carbon signals for the carbonyl groups in the ^{13}C nmr appear at 179 and 178 ppm, respectively. The detailed assignments of the ^{1}H and ^{13}C nmr spectra are listed in the experimental section.

EXPERIMENTAL SECTION

Melting points were uncorrected. The ir spectra were measured on a Perkin-Elmer 683 spectrometer. The ^{1}H (300 MHz) and ^{13}C (75 MHz) nmr spectra were recorded on a Varian VAX-300 spectrometer in $CDCl_3$. Elemental analyses were performed on a Carlo Erba 1106 analyzer.

2-Amino-3-chloro-1,4-naphthoquinone ***(2)***. A modified procedure described by Hoover and Day was used. 2,3-dichloro-1,4-naphthoquinone (15 g, 0.066 mol) was suspended in concentrated ammonium hydroxide (100 ml)and ethanol (300 ml). The mixture was gently refluxed for 90 min and during this period a slow stream of ammonia was passed into the solution. Nitrogen was then bubbled through the hot solution to remove the

ammonia and the solution was treated with decolorizing carbon and filtered. After standing overnight in a refrigerator, the product was filtered off, washed with water and dried to give **2** mp 195-196 ^{o}C (lit.,[18] 195-196 ^{o}C).

2-Phenyl-4,9-dioxonaphtho[2,3-*d*]selenazole (4a), General procedure: A mixture of selenium powder (0.16 g, 2 mmol), an excess of sodium (0.58 g, 25mmol) and naphthalene (0.60 g, 4.7mmol) in THF (6 ml) was refluxed for 1 h under nitrogen. After cooling, the unreacted sodium metal was removed by decantation. To this sodium selenide solution, 2-amino-3-chloro-1,4-naphthoquinone (0.42 g, 2 mmol) in DMF (25 ml) was added. The mixture was heated under nitrogen at 120^{o}C for 10 h to form a deep green solution. Benzaldehyde (0.53 g, 5 mmol) was added and the heating was continued for another 7 h. The hot solution was filtered and the filtrate was allowed to stand overnight at 0 ^{o}C. The resulting precipitate was collected by filtration and washed with ethanol. The crude product was purified by column chromatography (silica gel, $CHCl_3$) to give **4a**, 0.45 g, 66% yield (see Table 1). ^{1}H Nmr ($CDCl_3$): δ 8.30 (1H, dd, J = 8.1 and 2.0 Hz), 8.19 (1H, dd, J = 8.3 and 1.9 Hz), 7.89 (2H, d, J = 7.8 Hz), 7.80-7.75 (2H, m), 7.55-7.35 (3H, m); ^{13}C nmr: δ 179.6, 177.5, 155.8, 138.1, 133.8, 131.5, 129.3, 129.1, 128.1, 128.0, 127.3, 126.2, 124.8, 119.8; ir(KBr): 1690, 1670, 1600, 1585, 1052, 700 cm^{-1}.

2-(4-Tolyl)-4,9-dioxonaphtho[2,3-*d*]selenazole (4b). - ^{1}H Nmr($CDCl_3$): δ 8.23 (1H, dd, *J = 8.1 and 2.0 Hz*), 8.21 (1H, dd, J = 8.3 and 1.8 Hz), 7.96 (2H, d, J = 8.1), 7.80-7.76 (2H, m), 7.28 (2H, d, J = 8.3 Hz), 2.40 (3H, s, CH_3); ^{13}C nmr: δ 179.8, 177.9, 156.3, 143.3, 134.2, 133.7, 132.8, 132.7, 132.5, 129.9, 128.1, 127.7, 126.8, 21.6 (CH_3); ir(KBr):1685, 1660, 1620, 1600, 1500, 1040, 720 cm^{-1}.

2-(2-Tolyl)-4,9-dioxonaphtho[2,3-*d*]selenazole (4c). - ^{1}H Nmr(CDCl): δ 8.32 (1H, dd, J = 8.0 and 2.2 Hz), 8.21 (1H, dd, J = 7.9 and 2.0 Hz), 7.93 (1H, s), 7.83-7.76 (3H, m), 7.36 (2H, d, J = 5.2 Hz), 2.45 (3H, s, CH_3); ^{13}C nmr:δ 179.9, 177.8, 156.3, 139.2, 135.0, 134.2, 133.8, 133.2, 132.8, 132.7, 129.1, 128.4, 127.8, 126.8, 125.6, 21.1; ir(KBr): *1680, 1660, 1600, 1470, 720 cm*$^{-1}$.

2-(4-Methoxyphenyl)-4,9-dioxonaphtho[2,3-*d*]selenazole (4d). - ^{1}H Nmr($CDCl_3$): δ 8.32 (1H, d, J = 7.0 Hz), 8.21 (1H, d, J = 7.1 Hz), 8.04 (2H, d, J = 8.7 Hz), 7.80-7.76 (2H, m), 6.98 (2H, d, J = 8.7 Hz), 3.89 (3H, s, OCH_3); ir(KBr): 1695, 1660, 1620, 1595, 1470, 1020, 720 cm^{-1}.

2-(2-Methoxyphenyl)-4,9-dioxonaphtho[2,3-*d*]selenazole (4e). - ^{1}H Nmr($CDCl_3$): δ 8.68 (1H, dd, J = 7.9 and 1.8 Hz), 8.32 (1H, d, J = 9.0 Hz), 8.21 (1H, d, J = 9.0 Hz), 7.79-7.75 (2H, m), 7.54 (1H, td, J = 8.0 and 1.7 Hz), 7.15 (1H, t, J = 7.9 Hz), 7.09 (1H, d, J = 8.0 Hz), 4.14 (3H, s, OCH_3); ^{13}C nmr: δ 179.9, 178.6, 156.0, 139.8, 135.0, 133.9, 133.6, 133.1, 132.5, 128.9, 127.7, 126.7, 121.3, 111.2, 56.6 (OCH_3); ir(KBr): 1690, 1665, 1600, 1430, 1020, 715 cm^{-1}.

2-(4-Chlorophenyl)-4,9-dioxonaphtho[2,3-*d*]selenazole (4f). - ^{1}H Nmr($CDCl_3$): δ 8.34 (1H, dd, J = 8.0 and 2.0

Hz), 8.23 (1H, dd, J = 7.8 and 1.8 Hz), 8.03 (2H, d, J = 8.8 Hz), 7.83-7.79 (2H, m), 7.48 (1H, d, J = 8.8 Hz); ir(KBr): 1690, 1600, 1455, 1015, 720 cm^{-1}.

2-(2-Furan)-4,9-dioxonaphtho[2,3-*d*]selenazole (4g). - ^1H Nmr($CDCl_3$): δ 8.32 (1H, dd, J = 8.8 and 1.8 Hz), 8.22 (1H, dd, J = 9.0 and 2.0 Hz), 7.81-7.77 (2H, m), 7.67 (1H, d, J = 1.1 Hz), 7.45 (1H, d, J = 3.6 Hz), 6.65 (1H, m); ir(KBr): 1690, 1660, 1600, 1590, 1490, 1025, 715 cm^{-1}.

General procedure of the preparation of 2-amino-3-alkylseleno-1,4-naphthoquinone: The appropriate alkyl halide (2 mmol) was added to the deep green solution of **3** (2 mmol) in DMF (25 ml). The mixture was stirred at room temperature under nitrogen for a few minutes to an hour (see Table 1). The color of the solution was changed from green to red. The solution was poured into water (100 ml), and extracted with ether and the extract was washed with water. Removal of the solvent gave the crude product, which was purified by column chromatography (silica gel, ether). The yields of **5a-5f** and their analyses are listed in Table 1.

2-Amino-3-propylseleno-1,4-naphthoquinone (5a). - ^1H Nmr(DMSO-d_6): δ 7.97 (2H, d, J = 7.0 Hz), 7.81 (1H, m), 7.75 (1H, m), 7.28 (2H, br, NH_2), 2.79 (2H, J = 7.2 Hz, $SeCH_2$), 1.58 (2H, m, CH_2), 0.92 (3H, t, J = 6.9 Hz, CH_2); ^{13}C nmr: δ 179.1, 178.8, 152.3, 134.7, 133.2, 132.3, 130.1, 126.1, 126.0, 104.2, 28.8, 23.3, 14.2.

2-Amino-3-n-butylseleno-1,4-naphthoquinone (5b). - ^1H Nmr(DMSO-d_6): δ 7.99 (2H, d, J = 7.5 Hz), 7.82 (1H, t, J = 7.4 Hz), 7.76 (1H, t, J = 7.5 Hz), 7.40 (2H, br, NH_2), 2.81 (2H, t, J = 6.0 Hz, $SeCH_2$), 1.54 (2H, quart, J = 7.25 Hz, CH_2), 1.35 (2H, m, CH_2), 0.83 (3H, t, J = 7.4 Hz, CH_3); ^{13}C nmr: δ 179.1, 178.6, 152.3, 134.7, 133.2, 132.3, 130.1, 126.1, 126.0, 104.1.

2-Amino-3-s-butylseleno-1,4-naphthoquinone (5c). - ^1H Nmr(DMSO-d_6): δ 8.00 (2H, d, J = 7.6 Hz), 7.83 (1H, td, J = 7.5 and 1.4 Hz), 7.74 (1H, td, J = 7.5 and 1.5 Hz), 7.30 (2H, br, NH_2), 3.45 (1H, m, CH), 1.60 (2H, m, CH_2), 1.30 (3H, d, J = 6.8 Hz, CH_3), 0.94 (3H, t, J = 7.4 Hz, CH_3); ^{13}C nmr: δ 179.2, 178.8, 152.8, 134.7, 133.2, 132.3, 130.2, 126.2, 125.9, 104.7, 38.9, 30.2, 21.0, 12.0.

2-Amino-3-benzylseleno-1,4-naphthoquinone (5d). - ^1H Nmr(CDCl): δ 8.10 (2H, m), 7.70 (1H, t, J = 7.6 Hz), 7.63 (1H, t, J = 7.5 Hz), 7.23 (5H, s, Ph), 5.74 (2H, NH_2), 4.05 (2H, s, CH_2); ^{13}C nmr: δ 179.0, 178.4, 152.1, 134.9, 134.5, 133.4, 132.3, 128.5, 127.2, 126.5, 117.1, 104.8, 30.2.

2-Amino-3-allylseleno-1,4-naphthoquinone (5e). - ^1H Nmr(CDCl): δ 8.12 - 8.03 (2H, m), 7.72 - 7.60 (2H, m), 5.45 (1H, m), 5.30 (2H, br, NH_2), 4.80 (1H, d, J = 8.0 Hz), 4.71 (1H, m), 3.50 (2H, d, J = 7.85 Hz, CH_2).

2-Amino-3-methoxycarbonylmethyl-1,4-naphthoquinone (5f). - ^1H Nmr(CDCl): δ 8.14 (2H, m), 7.68 (2H, m), 6.23 (2H, br, NH_2), 3.66 (3H, s, OCH_3), 3.49 (2H, s, CH_2); ^{13}C nmr: δ 179.2, 178.7, 152.2, 134.9, 133.6, 132.5, 127.3, 126.6, 105.0, 52.6, 26.2.

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