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REACTION OF 2,3-DICHLORO-1,4-NAPHTHOQUINONE WITH SOME ACTIVE METHYLENE COMPOUNDS IN DIFFERENT BASIC MEDIA

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Reaction of 2,3-dichloro-1,4-naphthoquinone with some active methylene compounds, such as malononitrile and cyanoacetamide, under various basic conditions has been investigated. A mechanism for these reactions is proposed.

Keywords: 2-anilino-3-chloro-1,4-naphthoquinone, cyanoacetamide, 2,3-dichloro-1,4-naphthoquinone, malononitrile.

In continuation of our work on the preparation of heterocyclic quinone derivatives [1-9], this part of our studies was focused on the reaction of 2,3-dichloro-1,4-naphthoquinone **1** with some active methylenes including malononitrile and cyanoacetamide.

2,3-Dichloro-1,4-naphthoquinone (**1**) reacts with malononitrile in equimolar ratios in the presence of an equivalent amount of sodium ethoxide at room temperature and ethanol as reaction medium to give a blue product. This product was formulated as (2,3-dichloro-4-hydroxy-1-oxo-1,2-dihydro-2-naphthalenyl)-propanedinitrile (**2**), based on its elemental analysis and IR spectrum.

However, on carrying out the above reaction in refluxing ethanol, two different products were formed which were separated by column chromatography. The first eluted substance was identified as (2-chloro-3-ethoxy-4-hydroxy-1-oxo-1,2-dihydro-2-naphthalenyl)propanedinitrile (**3**) and the other product was identified as dinitrile **2**. Compound **3** is expected to be formed via **2** since the reaction of the latter with sodium ethoxide gave **3** in 42% yield (Scheme 1). Formation of compound **3** proceeded *via* i) 1,4-Michael addition of malononitrile to **1** to give **2**, ii) an S_N2 displacement of the less sterically hindered chlorine atom by the ethoxide anion. Elemental analysis and spectral data established the chemical structure of **3**.

Refluxing **1** with malononitrile in ethanol in the presence of triethylamine as a catalyst gives the same product **3** obtained from the reaction of **1** with malononitrile in the presence of sodium ethoxide. This compound was identified from mp and mmp, elemental, and IR spectral analyses (finger print). By repeating the former reaction in dry toluene in the presence of triethylamine as a base, it gives (2-chloro-4-hydroxy-1-oxo-3-triethylammonio-1,2-dihydro-2-naphthalenyl)propanedinitrilecarbanion (**4**) (Scheme 2). Elemental analysis as well as spectral data established the chemical structure of **4**.

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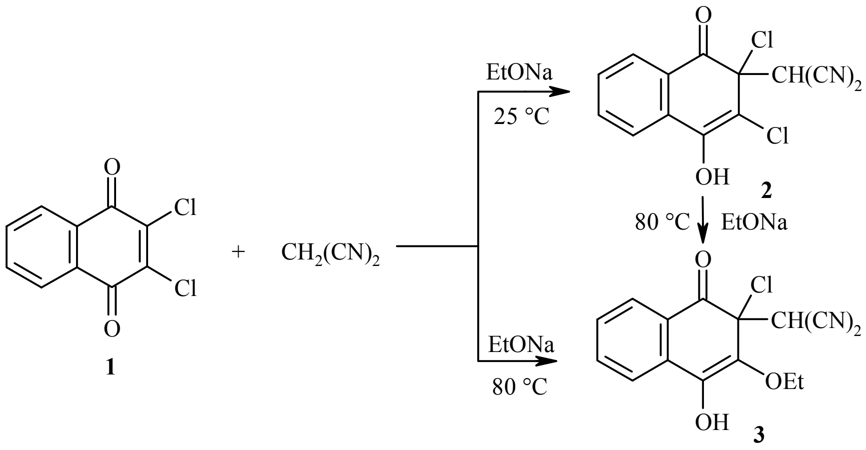
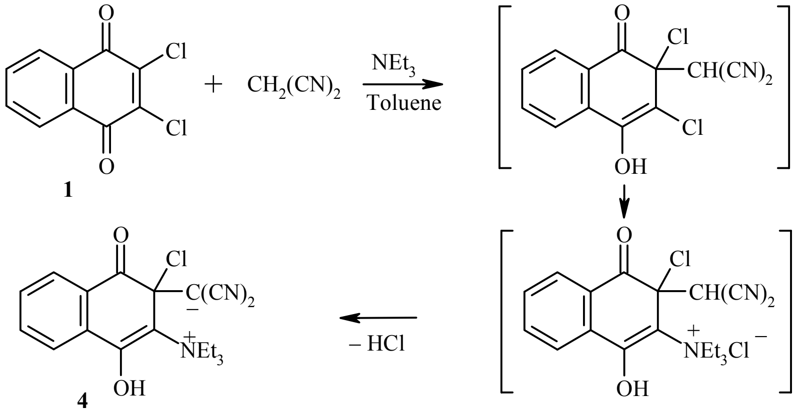
Scheme 1



Scheme 2



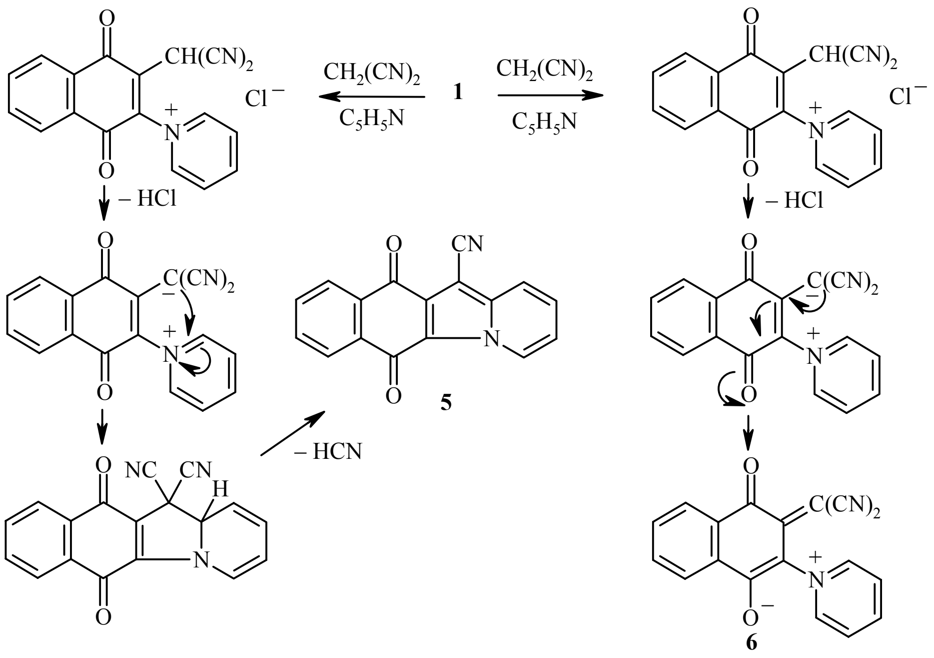
To complete the studies of the reactions of **1** with malononitrile in different basic media, we carried out its reaction with malononitrile in ethanol in the presence of pyridine in order to synthesize the target product **5.** The only product formed from this reaction was identified as 2-dicyanomethylene-1-oxo-3-pyridinio-4-naphtholate (**6**) instead of **5** (Scheme 3).

The structure of compound **6** has been firmly established from both elemental analysis and infrared spectral analyses.

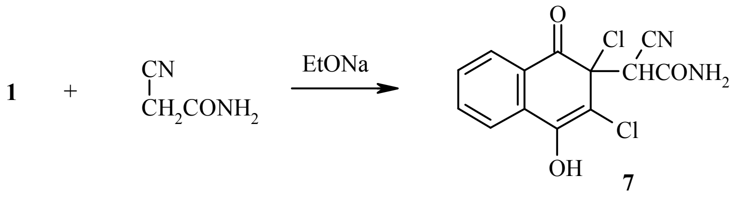
Treatment of dichloroquinone **1** with malononitrile in ethanol in the presence of quinoline as a base gives greenish yellow crystals, identified as (2-chloro-3-ethoxy-4-hydroxy-1-oxo-1,2-dihydro-2-naphthalenyl)propanedinitrile (**3**) based on mp and mmp, elemental and IR spectral analyses.

Treatment of compound **1** with cyanoacetamide in ethanol in the presence of an equivalent amount of sodium ethoxide afforded α-(2,3-dichloro-4-hydroxy-1-oxo-1,2-dihydro-2-naphthalenyl)-α-cyanoacetamide (**7**) (Scheme 4). The confirmation of structure **7** was based on its elemental and IR spectral analyses.

Scheme 3

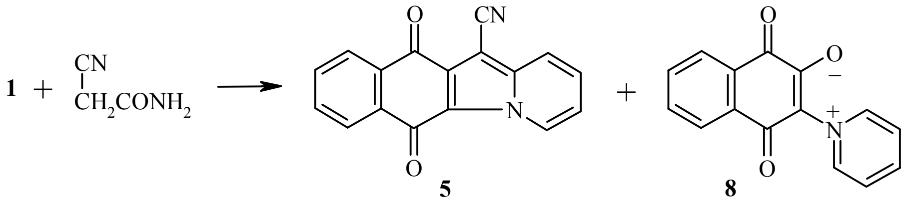


Scheme 4



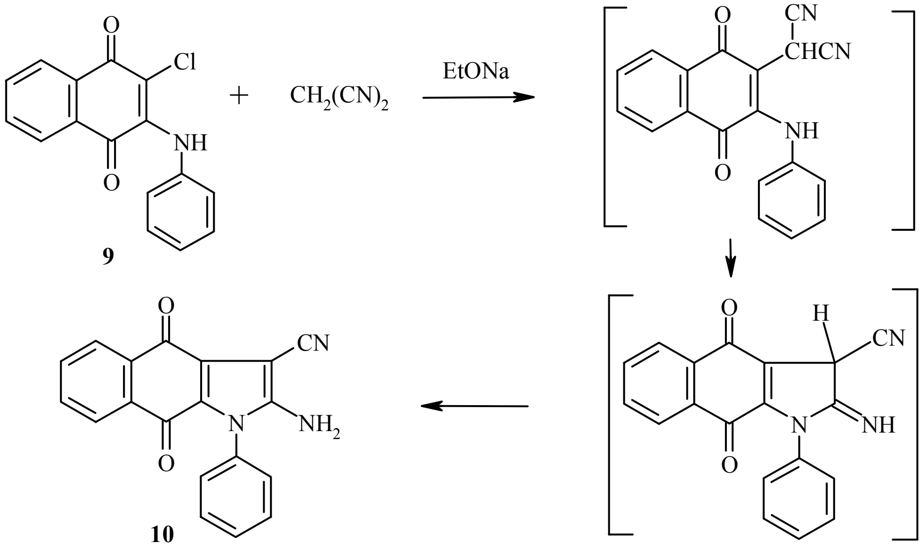
In this investigation the reaction of 2,3-dichloro-1,4-naphthoquinone **1** with active methylenes in different basic media were continued to include the reaction of **1** with cyanoacetamide in ethanol and in the presence of pyridine as a base which afforded 12-cyanonaphth[2,3-*b*]indolizine-6,11-dione (**5**) and betaine salt **8** (Scheme 5). The chemical structure of compound **5** was established by elemental and spectral analyses.

Scheme 5



When **1** was replaced by 2-anilino-3-chloro-1,4-naphthoquinone (**9**) in order to see the effect of the anilino group on the mode of the reaction with malononitrile in the presence of sodium ethoxide, a dark green product was separated by column chromatography in a very low yield (2%), which was identified as 2-amino-4,9-dioxo-4,9-dihydro-1-phenyl-1H-benz[*f*]indole-3-carbonitrile (**10**) (Scheme 6). The structure of **10** was established by elemental and spectral analyses.

Scheme 6



EXPERIMENTAL

All the analyses were carried out at the Organic Chemistry Department, Regensburg University, Germany. Melting points were measured using an SMP-20 melting point apparatus and were uncorrected. The IR spectra were recorded on an Acculab 1 (Beckman) using the KBr pellet technique. The ^{1}H NMR spectra were run on a WH-250-PFT NMR spectrometer (250 MHz); chemical shifts are reported in ppm with TMS as an internal standard. Electron impact mass spectra were obtained at 70 eV using a monofocusing Varian MAT CH-5 mass spectrometer. Elemental analyses were done on a CHN-Rapid U/E (Heraeus) instrument.

(2,3-Dichloro-4-hydroxy-1-oxo-1,2-dihydro-2-naphthalenyl)propanedinitrile (2). To a solution of pure sodium (0.12 g, 5 mmol) in superdried ethyl alcohol (50 ml) is added malononitrile (0.33 g, 5 mmol) slowly with stirring. To the resulting clear solution is added gradually 2,3-dichloro-1,4-naphthoquinone (0.14 g, 5 mmol). Reaction occurs almost immediately with the formation of an intense blue colored solution, stirring was continued for 6 h at room temperature. The solution was filtered off and the filtrate was concentrated and cooled; a blue crystalline product precipitated which was collected and recrystallized from ethanol to give nitrile **2** as blue microcrystals; mp >300°C, yield 850 mg (58%). IR spectrum (KBr), ν, cm^{-1}: 1680 (CO), 2220 (CN), 3480 (OH). ^{1}H NMR spectrum (DMSO-d$_6$), δ, ppm: 3.46 (1H, s, H_{sp^3}); 7.58-7.90 (4H, m, Ar) and 9.98 (1H, s, OH). Found, %: C 53.52; H 1.94; N 9.78. $C_{13}H_6Cl_2N_2O_2$. Calculated, %: C 53.27; H 2.06; N 9.56.

(2-Chloro-3-ethoxy-4-hydroxy-1-oxo-1,2-dihydro-2-naphthalenyl)propanedinitrile (3). The above reaction was carried out by heating under reflux for 6 h, and the crude material was separated by column chromatography into two products using methylene chloride and acetonitrile (1:1) as a eluent. The first compound was recrystallized from ethanol to give **3** as greenish yellow fine crystals, mp >300°C, yield 270 mg (18%). The other compound was identified as **2** and were blue microcrystals; mp >300°C, yield 480 mg (33%). IR spectrum (KBr), ν, cm^{-1}: 1670 (CO); 2220 (CN); 3060 (OH). ^1H NMR spectrum (DMSO-d_6), δ, ppm, *J* (Hz): 1.05 (3H, t, *J* = 7, CH_3); 3.37 (2H, q, *J* = 7, CH_2); 3.41 (1H, s, H_{sp^3}); 7.62-7.95 (4H, m, Ar) and 9.94 (1H, s, OH). Mass spectrum, *m/z* (*I*, %): 302 ($M^{+\cdot}$, 19.31, ^{35}Cl), 304 ($M^{+\cdot}$, 6.81, ^{37}Cl), 239 (100). Calculated: M 302.71. Found, %: C 59.54; H 3.85; N 9.23. $C_{15}H_{11}ClN_2O_3$. Calculated, %: C 59.52; H 3.66; N 9.25.

Reaction of (2,3-Dichloro-4-hydroxy-1-oxo-1,2-dihydro-2-naphthalenyl)propanedinitrile (2) with Sodium Ethoxide. A mixture of **2** (1.46 g, 5 mmol) and pure sodium metal (0.12 g, 5 mmol) in superdried ethyl alcohol (60 ml) was refluxed for 12 h. The reaction mixture was then filtered hot to separate the precipitated sodium chloride. The filtrate was concentrated to about half of its volume and cooled, and the precipitated product was collected and recrystallized from ethanol to give **3** as greenish yellow fine crystals; mp >300°C, yield 0.63 g (42%). IR and mass spectra are identical to those mentioned above. Elemental analysis data are consistent with chemical formula of **3**.

Reaction of 2,3-Dichloro-1,4-naphthoquinone with Malononitrile in Ethanol and Triethylamine. To a mixture of 2,3-dichloro-1,4-naphthoquinone (1.14 g, 5 mmol) and malononitrile (0.33 g, 5 mmol) in absolute ethanol (50 ml) was added with stirring triethylamine (5 ml). Reaction occurs almost immediately with the formation of an intense blue colored solution. The reaction mixture was heated under reflux for 12 h with continuous stirring, then concentrated and cooled. The precipitate was collected by filtration; it contained a mixture of the starting material and the product as tested by TLC using chloroform–ethanol (1:1) as eluent. The product was purified from DCNQ **1** by extracting the latter with hot toluene (50 ml); it was then recrystallized from toluene–ethanol (1:1) to give (2-chloro-3-ethoxy-4-hydroxy-1-oxo-1,2-dihydro-2-naphthalenyl)-propanedinitrile (**3**) as greenish yellow fine crystals; mp >300°C, yield 600 mg (20%). IR spectrum (KBr), ν, cm^{-1}: 1670 (CO); 2220 (CN); 3060 (OH).

(2-Chloro-4-hydroxy-1-oxo-3-triethylammonio-1,2-dihydro-2-naphthalenyl)propanedinitrilecarbanion (4). The former reaction was carried out in dry toluene (50 ml) and triethylamine (5 ml) with stirring (6 h) at room temperature. A blue precipitate was formed which was filtered off and recrystallized from methylene chloride to give zwitterion **4** as violet plates; mp 141-142°C, yield 900 mg (50%). IR spectrum (KBr), ν, cm^{-1}: 1670 (CO); 2200 (CN); 3500 (OH). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 1.20 (9H, t, $3CH_3$); 3.12 (6H, q, $3CH_2$); 7.66-7.97 (4H, m, Ar) and 8.89 (1H, br. s, OH). Mass spectrum, *m/z* (*I*, %): 256 ($M^{+\cdot}$, 1.21, ^{35}Cl), 258 ($M^{+\cdot}$, 0.80, ^{37}Cl) 86(100). Calculated M 357.83. Found, %: C 63.74; H 5.74; N 11.62. $C_{19}H_{20}ClN_3O_2$. Calculated, %: C 63.77; H 5.63; N 11.74.

2-Dicyanomethylene-1-oxo-3-pyridinio-4-naphtholate (6). When 5 ml of pyridine was substituted for triethylamine in the above reaction, under the same conditions, a reddish violet solution was obtained, which was concentrated and cooled. The precipitated product was collected and recrystallized from ethanol to give **6** as reddish violet needles; mp 306°C (Lit. [10] mp 305°C), yield 1.10 g (74%). IR spectrum (KBr), ν, cm^{-1}: 1680 (CO); 2220 (CN). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 7.76-7.91 (4H, m, Ar); 8.75 (1H, dd); 8.30 (2H, dd) and 9.09 (2H, d) of pyridinium. Mass spectrum, *m/z* (*I*, %): 300 ($M^{+\cdot}$ + 1, 21.10), 299 ($M^{+\cdot}$, 100). Calculated: M 299.28. Found, %: C 72.23; H 3.31; N 14.03. $C_{18}H_9N_3O_2$. Calculated, %: C 72.24; H 3.03; N 14.04.

Reaction of 2 with Malononitrile in Ethanol and Quinoline. Repeating the former reaction using 5 ml of quinoline as a base substituted for pyridine, an intense blue colored solution was obtained, which changed to a greenish yellow color upon continuous heating under reflux for 12 h. The solution was concentrated and cooled and the substance was collected and recrystallized from a mixture (1:1) toluene–ethanol to give **3** as greenish yellow crystals, mp >300°C, yield 400 mg (26%). IR spectrum (KBr), ν, cm^{-1}: 1670 (CO); 2220 (CN); 3060 (OH).

α-(2,3-Dichloro-4-hydroxy-1-oxo-1,2-dihydro-2-naphthalenyl)-α-cyanoacetamide (7). To a solution of sodium metal (0.12 g, 5 mmol) in dried ethanol (50 ml) is added cyanoacetamide (0.42 g, 5 mmol). To the resulting solution is added 2,3-dichloro-1,4-naphthoquinone (1.14 g, 5 mmol). An orange color formed at the beginning, then turned into greenish, then to violet. The reaction mixture was refluxed for 6 h and filtered while hot; concentration and cooling of the filtrate gave a violet precipitate, which was recrystallized from ethanol to give **7** as violet needles; mp >300°C, yield 800 mg (52%). IR spectrum (KBr), ν, cm^{-1}: 1650 (CO); 1690 (CO); 2200 (CN); 3290, 3400 (NH_2); 3460 (OH). Mass spectrum, *m/z* (*I*, %): 311 ($M^{+\cdot}$, 14.37); (86, 100). Calculated: M 311.11. Found, %: C 49.92; H 2.79; N 8.86. $C_{13}H_8Cl_2N_2O_3$. Calculated, %: C 50.18; H 2.59; N 9.00.

12-Cyanonaphth[2,3-*b*]indolizine-6,11-dione (5). To a mixture of **1** (1.14 g, 5 mmol) and cyanoacetamide (0.42 g, 5 mmol) in 50 ml of absolute ethanol was added with stirring pyridine (5 ml); a greenish yellow color was formed. The reaction mixture was heated under reflux for 4 h then concentrated to half of its volume and cooled. The precipitated solid was collected by filtration, washed with a little absolute ethanol, dried, and purified by column chromatography on silica gel, using methylene chloride–ethanol (2:1) as an eluent. The first red band eluted afforded after evaporation a yellowish red solid, crystallized from ethanol as microplates of **5** [10]; mp >300°C, yield 200 mg (15%). The second orangish yellow band afforded **8**, which was crystallized from ethanol as orangish yellow needles; mp 305°C (Lit. [11] 305°C), yield 600 mg (48%). IR spectrum (KBr), ν, cm^{-1}: 1650 (CO); 2210 (CN). ^{1}H NMR spectrum (DMSO-d$_6$), δ, ppm: 7.52, 7.74 (2H, 2d, H-1,3); 7.84-7.94, 8.05-8.20 (5H, 2m, Ar + H-2) and 9.65 (1H, d, H-4). Found, %: C 74.88; H 3.10; N 10.06. $C_{17}H_8N_2O_2$. Calculated, %: C 74.99; H 2.96; N 10.28

2-Amino-4,9-dioxo-4,9-dihydro-1-phenyl-1H-benz[*f*]indole-3-carbonitrile (10). To a solution of sodium metal (0.12 g, 5 mmol) in absolute ethanol (50 ml) malononitrile (0.33 g, 5 mmol) is added. To the resulting solution is added gradually over a period of 20 min 2-anilino-3-chloro-1,4-naphthoquinone (**9**) (1.42 g, 5 mmol). The reaction mixture was heated under reflux for 48 h; during this time a green color developed and reached its maximum intensity. The reaction mixture was then filtered hot to separate the precipitated NaCl. The filtrate was concentrated and cooled, leaving a resinous material, which was purified using column chromatography (silica gel with chloroform as an eluent). The first fraction obtained was identified as the starting material. The second fraction afforded a green substance, which was crystallized from methylene chloride and identified as nitrile **10**; mp >300°C, yield 30 mg (2%). IR spectrum (KBr), ν, cm^{-1}: 1690 (CO); 2200 (CN); 3200, 3400 (NH_2). ^{1}H NMR spectrum (DMSO-d$_6$), δ, ppm: 7.38-8.00 (9H, m, Ar) and 10.00 (2H, broad s, NH_2). Found, %: C 72.69; H 3.61; N 13.82. $C_{19}H_{11}N_3O_2$. Calculated, %: C 72.83; H 3.54; N 13.41.

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