Synthesis of Naphthofuran-3-spirocyclohexanetriones

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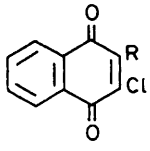
The condensation of 2,3-dichloro-1,4-naphthoquinone with nitrocyclohexane and t-butyl cyclohexanecarboxylate has been studied. The product resulting from reaction of the quinone with t-butyl cyclohexanecarboxylate, 3-chloro-2-(1-t-butoxycarbonylcyclohexyl)-1,4-naphthoquinone (3), was readily hydrolysed to the corresponding acid (4). Thermal cyclisation of this compound gave rise to the two isomeric quinone lactones naphtho[2,3-*b*]furan-3-spirocyclohexane-2,4,9(3*H*)-trione (8) and naphtho[1,2-*b*]-furan-3-spirocyclohexane-2,4,5(3*H*)-trione (10). Procedures were devised which allowed either (8) or (10) to be obtained exclusively.

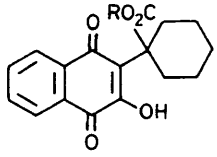
The base-induced reaction of a wide variety of active-methylene compounds with 2,3-dichloro-1,4-naphthoquinone (DNQ) has been extensively studied. To our knowledge in all the examples reported to date, the carbon nucleophile employed has contained two electron-withdrawing groups. For example, ethyl acetoacetate [1,2] condenses with DNQ to give (1) whilst indan-1,3-dione [3] yields (2).

In a continuation of our interest in naphthoquinone chemistry [4] we have investigated the reaction of DNQ with cyclohexane derivatives containing just one electron-withdrawing group, *i.e.* nitrocyclohexane and t-butyl cyclohexanecarboxylate. In the latter case it was envisaged that the resulting product (3) should hydrolyse to a quinone (4) which could formally be considered a vinylogous β-keto-acid. Hence, this might undergo facile decarboxylation to 2-chloro-3-cyclohexyl-1,4-naphthoquinone (5) which, in turn, could be converted into 2-cyclohexyl-3-hydroxy-1,4-naphthoquinone—a compound of interest because of its activity against the cattle parasite *Theileria parva*.[4] In the event, although (4) was readily obtained its thermal decarboxylation to (5) could not be induced. Instead two isomeric quinone lactones were formed.

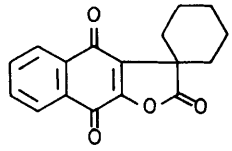
The structure of these compounds and their associated chemistry is reported herein.



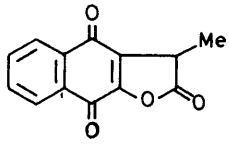
(1) R = —CH(Ac)·CO_2Et
(2) R = 1,3—dioxoindan—2—yl
(3) R = —C(CO_2Bu^t)·$[CH_2]_4$·CH_2
(4) R = —C(CO_2H)·$[CH_2]_4$·CH_2
(5) R = —CH·$[CH_2]_4$·CH_2
(6) R = —C(NO_2)·$[CH_2]_4$·CH_2



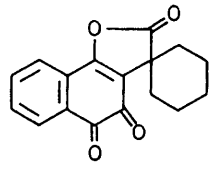
(7) R = Bu^t
(11) R = H



(8)



(9)



(10)

Results and Discussion

Initially, the reaction of DNQ and t-butyl cyclohexanecarboxylate was studied in the presence of lithium di-isopropyl amide. The expected product (3) was obtained but only in low yield (6%). Substantial quantities of the starting quinone and 2-chloro-3-hydroxy-1,4-naphthoquinone were also isolated. Variation of the reaction time and temperature resulted only in the yield increasing at best to 10%. However, when the reaction was carried out in the presence of lithium dicyclohexylamide the yield of (3) rose to 50%. A similar condensation using nitrocyclohexane gave rise to (6) in 16% yield. No attempt was made to optimise the yield of this product.

The t-butyl ester (3) was smoothly hydrolysed to the corresponding carboxylic acid (4) with hydrochloric acid in either ethanol (62% yield) or dimethoxyethane (94%). Selective hydrolysis of the chloro-group of (3) with methanolic potassium hydroxide solution gave the hydroxyquinone (7) in high yield (91.5%).

During the melting point determination of (4) decomposition with gas evolution was observed at 163 °C. On the basis of tests with pH indicator papers and barium hydroxide solution it was concluded that this gas was hydrogen chloride and not carbon dioxide. When (4) was heated under nitrogen at 175 °C until gas evolution ceased a product was isolated the analysis for which corresponded to the molecular formula $C_{17}H_{14}O_4$. The i.r. spectrum showed prominent carbonyl absorption at 1 820 (lactone), 1 678 and 1 662 cm^{-1} (naphthoquinone) whilst the ^1H n.m.r. spectrum revealed signals due to five methylene groups (cyclohexyl ring) and four aromatic protons. The latter were observed as two complex multiplets at δ 8.1 and 7.8, each integrating for two protons. On the basis of this evidence the compound was assigned the lactone structure (8). Only one related compound (9) appears to have been reported in the literature [5] and in this case the structure was not definitely established.

Examination of the reaction mixture from which (8) was obtained showed the presence of material which by t.l.c. was slightly more polar. Preliminary attempts to obtain this material free from (8) were unsuccessful. However, treatment of the ester (3) in refluxing benzene with toluene-*p*-sulphonic acid unexpectedly gave this compound in 64% yield with no trace of the lactone (8). The reaction was concluded to have occurred *via* the acid (4) since treatment of the latter under similar conditions also gave the same product. As with (8), the

unknown compound had an analysis corresponding to $C_{17}H_{14}O_4$. Carbonyl absorption was seen in the i.r. spectrum at 1 820 (lactone) and 1 662 cm^{-1} (quinone). However, a band seen at 720 cm^{-1} in the spectrum of compounds (3)—(8), apparently characteristic of unsymmetrically substituted 1,4-naphthoquinones,[6] was absent. The ^1H n.m.r. showed signals due to the cyclohexyl methylene groups and to four aromatic protons. The latter were observed as signals at δ 8.25 (1 H) and δ 7.7 (3 H). From this the compound was deduced to be the 1,2-naphthoquinone isomer of (8), *i.e.* (10). Supporting evidence for this assignment was provided by mass spectra (C.I.). It is known that 1,2-quinones have a pronounced tendency to form $(M + 2)^+$ peaks in contrast to 1,4-quinones.[7] In the spectrum of (10) a prominent $M + NH_3$ peak at *m/z* 302 was observed whereas the corresponding molecular ion from (8) was seen at *m/z* 300.

Hydrolysis of the quinone lactone (10) with base gave 2-(1-carboxycyclohexyl)-3-hydroxy-1,4-naphthoquinone (11). When this compound was heated at 180 °C for several minutes the 1,4-naphthoquinone lactone (8) was formed in good yield. Unlike the preparation of (8) from (4) no sign of the isomer (10) was observed.

Experimental

M.p.s, uncorrected, were recorded using an Electrothermal capillary tube melting-point apparatus. I.r. spectra were measured as KBr discs on a Perkin Elmer 157G spectrometer. N.m.r. spectra were determined using a Bruker HFX-90, Varian HA-100 or T-60 spectrometer for solutions in deuteriochloroform with tetramethylsilane as internal standard. Mass spectra (C.I.) were obtained with a VG micromass 7070F spectrometer operating at 50 eV with ammonia as the ionising gas. T.l.c. was carried out with Merck GF 254 silica gel plates using toluene–ethyl acetate (1 : 1). Light petroleum refers to the fraction of b.p. 60—80 °C.

3-*Chloro*-2-(1-*t-butoxycarbonylcyclohexyl*)-1,4-*naphthoquinone* (3).—Dicyclohexylamine (5.43 g, 30 mmol) in dry tetrahydrofuran (10 ml) was added dropwise under nitrogen to a vigorously stirred solution (1.6M) of butyl-lithium in hexane (20 ml, 32 mmol) at −10 °C. The solution was then kept at 0 °C for 15 min before being cooled to −70 °C. t-Butyl cyclohexanecarboxylate (4.6 g, 25 mmol) in tetrahydrofuran (10 ml) was added during 30 min and the resulting mixture further stirred at −70 °C for 1.5 h until a clear solution was formed. 2,3-Dichloro-1,4-naphthoquinone (5.67 g, 25 mmol) in tetrahydrofuran (130 ml) was then added during 30 min and the resulting dark green solution maintained initially at −70 °C for 1 h and then at −35 °C for 1 h. Finally the solution was stirred at room temperature overnight before being diluted with ethyl acetate and washed with water. The ethyl acetate was dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as a slightly sticky brown solid (9.98 g). This was crystallised from toluene–light petroleum (4 : 1) (150 ml) to give (3) as bright yellow crystals (4.13 g, 44%), m.p. 150—152 °C. A further 0.5 g (5.5%) of product was recovered from the filtrate (Found: C, 67.25; H, 5.9. $C_{21}H_{23}ClO_4$ requires C, 67.28; H, 6.19%); δ 1.62 (9 H, s, CMe_3), 1.62—2.8 (10 H, m, 5 × CH_2), 7.82 (2 H, m, ArH), and 8.1 (2 H, m, ArH); $\nu_{max.}$ 1 745, 1 685, and 1 675 cm^{-1}.

2-*Chloro*-3-(1-*nitrocyclohexyl*)-1,4-*naphthoquinone* (6).—Similar experimental conditions were employed as in the preparation of (3), nitrocyclohexane (3.22 g, 25 mmol) being used in place of t-butyl cyclohexanecarboxylate. The crude product (8.0 g) was crystallised from toluene–light petroleum (1 : 2) (150 ml) to give pure product (6) as yellow crystals (1.3 g, 16%), m.p. 132—134 °C (Found: C, 60.4; H, 4.45; N, 4.4. $C_{16}H_{14}ClNO_4$ requires C, 60.10; H, 4.41; N, 4.38%); δ 1.7 (6 H, m, 3 × CH_2), 2.6 [4 H, m, $CH_2{\cdot}C(NO_2){\cdot}CH_2$], and 7.6—8.2 (4 H, m, ArH).

3-*Hydroxy*-2-(1-*t-butoxycarbonylcyclohexyl*)-1,4-*naphthoquinone* (7).—3-Chloro-2-(1-t-butoxycarbonylcyclohexyl)-1,4-naphthoquinone (3) (1.0 g, 2.67 mmol) was dissolved in boiling methanol (20 ml) and potassium hydroxide (1.0 g) in water (10 ml) was added dropwise. After being heated under reflux for 20 min the dark red solution was cooled in ice, vigorously stirred, and acidified with concentrated hydrochloric acid. The precipitated solid was filtered off, washed with water, and dried *in vacuo* to give the desired product as a yellow solid (0.87 g, 91.5%), m.p. 140—142 °C (Found: C, 70.6; H, 6.7. $C_{21}H_{24}O_5$ requires C, 70.77; H, 6.79%); δ 1.4 (15 H, m, CMe_3, 3 × CH_2), 2.1 [4 H, m, $CH_2{\cdot}C(CO){\cdot}CH_2$], 7.6 (2 H, m, ArH), and 7.9 (2 H, m, ArH); $\nu_{max.}$ 3 360, 1 745, 1 730, 1 670, and 1 660 cm^{-1}.

2-(1-*Carboxycyclohexyl*)-3-*chloro*-1,4-*naphthoquinone* (4).—(a) 3-Chloro-2-(1-t-butoxycarbonylcyclohexyl)-1,4-naphthoquinone (3) (100 mg, 0.367 mmol) was dissolved in dimethoxyethane (3 ml) and 6M-hydrochloric acid added (2 ml). The resulting solution was heated at reflux for 1 h, cooled in ice, and the precipitated solid filtered off, washed with water, and dried to give (4) (80 mg, 94%), decomposing at 163—165 °C (Found: C, 64.25; H, 4.85. $C_{17}H_{15}ClO_4$ requires C, 64.05; H, 4.74%), $\nu_{max.}$ 3 380, 1 750, 1 680, and 1 670 cm^{-1}.

(b) The naphthoquinone (3) (1.0 g, 2.67 mmol) was dissolved in ethanol (50 ml) and concentrated hydrochloric acid (10 ml) added. The resulting solution was heated at reflux for 1 h, diluted with water (200 ml), and extracted with chloroform (2 × 100 ml). The chloroform solution was washed with water and extracted with aqueous sodium hydrogen carbonate (10%; 100 ml). The sodium hydrogen carbonate solution was acidified (hydrochloric acid) and the resulting mixture extracted with chloroform (100 ml). The extract was dried and evaporated to afford (4) as a yellow solid (0.53 g, 62%), decomposing at 161—163 °C (Found: C, 63.9; H, 4.8. $C_{17}H_{15}ClO_4$ requires C, 64.05; H, 4.74%).

Naphtho[2,3-b]*furan*-3-*spirocyclohexane*-2,4,9(3H)-*trione* (8).—(a) *From* 2-(1-*carboxycyclohexyl*)-3-*chloro*-1,4-*naphthoquinone* (4). The quinone (4) (1.3 g, 4.08 mmol) was heated under nitrogen in an oil-bath maintained at 175—180 °C. After 15 min when HCl evolution had ceased the resulting solid was crystallised from ethanol to give the lactone (8) as yellow needles (0.4 g, 35%), m.p. 183—184 °C (Found: C, 72.25; H, 5.0. $C_{17}H_{14}O_4$ requires C, 72.33; H, 5.00%), δ 1.5—2.4 (10 H, m, 5 × CH_2), 7.8 (2 H, m, ArH), and 8.1 (2 H, m, ArH); $\nu_{max.}$ 1 820, 1 678, and 1 622 cm^{-1}. The filtrate was shown by t.l.c. to contain both (8) and (10).

(b) *From* 2-(1-*carboxycyclohexyl*)-3-*hydroxy*-1,4-*naphthoquinone* (11). The quinone (11) (0.6 g, 2 mmol) was heated at 180 °C for 15 min. Crystallisation of the resulting solid from ethanol gave the desired product (0.42 g, 74%), m.p. 183—184 °C (Found: C, 72.1; H, 5.0. $C_{17}H_{14}O_4$ requires C, 72.33; H, 5.00%). T.l.c. of this product (and of the filtrate) showed the absence of (10).

Naphtho[1,2-b]*furan*-3-*spirocyclohexane*-2,4,5(3H)-*trione* (10).—(a) *From* 2-(1-t-*butoxycarbonylcyclohexyl*)-3-*chloro*-1,4-*naphthoquinone* (3). The quinone (3) (1.0 g, 2.67 mmol) was dissolved in benzene (20 ml) containing toluene-*p*-sulphonic acid monohydrate (0.3 g). The solution was heated under reflux for 20 min, cooled in ice, and the precipitated orange solid (0.7 g) filtered off and dried. T.l.c. examination of both

solid and filtrate showed (10) to be present and (8) absent. The solid [(10) + toluene-*p*-sulphonic acid] was crystallised from ethyl acetate to give (10) as orange crystals (0.48 g, 64%), m.p. 254—256 °C (Found: C, 71.95; H, 5.05. $C_{17}H_{14}O_4$ requires C, 72.33; H, 5.00%), δ 1.4—2.4 (10 H, m, 5 × CH_2), 7.7 (3 H, m, ArH), and 8.25 (H, m, ArH); $\nu_{max.}$ 1 820 and 1 668 cm^{-1}.

(b) *From* 2-(1-*carboxycyclohexyl*)-3-*chloro*-1,4-*naphthoquinone* (4). The quinone (4) (50 mg, 157 mmol) and toluene-*p*-sulphonic acid monohydrate (15 mg) were heated in refluxing benzene (1 ml) for 20 min. The orange solution was then cooled in ice and the precipitated solid filtered off and crystallised from ethyl acetate (3 ml) to give the desired product as orange crystals (30 mg, 68%), m.p. 255—256 °C. T.l.c. of the filtrate showed the absence of (8).

2-(1-*Carboxycyclohexyl*)-3-*hydroxy*-1,4-*naphthoquinone* (11). —The trione (10) (1.46 g, 5.18 mmol) was stirred with 2M-NaOH (75 ml) at room temperature overnight. The deep red solution was then acidified (hydrochloric acid) and the resulting precipitate filtered off, washed with water, and dried to yield a yellow solid (1.42 g, 91%) which was crystallised from toluene; it had m.p. 174—176 °C (Found: C, 68.05; H, 5.45. $C_{17}H_{16}O_5$ requires C, 68.00; H, 5.33%); δ 1.5 (6 H, m, 3 × CH_2), 2.25 [4 H, m, $CH_2{\cdot}C(CO_2H){\cdot}CH_2$], 7.75 (2 H, m, ArH), and 8.20 (2 H, m, ArH); $\nu_{max.}$ 3 360, 1 705, and 1 655 cm^{-1}.

Acknowledgement

We are indebted to Dr. A. J. Everett and his staff for spectroscopic and microanalytical data.

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Received 8*th April* 1982; *Paper* 2/606