Intramolecular Acetalisation of Naphthoquinones

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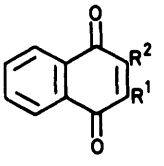
Attempts have been made to synthesise the glyceride quinone 2-cyclohexyl-3-(1,2-dihydroxyethyl)methoxy-1,4-naphthoquinone (3) as a prodrug of 2-cyclohexyl-3-hydroxy-1,4-naphthoquinone (4). The intermediate 2-cyclohexyl-3-(2,2-dimethyl-1,3-dioxolan-4-yl methoxy)-1,4-naphthoquinone (6), required for the projected synthesis, was readily obtained. However, on acid treatment this compound unexpectedly furnished 5-cyclohexyl-10b,2-epoxymethano- (7) and 5-cyclohexyl-10b,3-epoxymethano-2,3-dihydronaphtho[1,2-*b*]dioxin-6(10b*H*)-one (8). The structures of these compounds have been established by spectroscopic and degradative studies and a mechanism is proposed to account for their formation.

In an attempt to modify the pharmacokinetic properties of the antiparasitic 2-alkyl-3-hydroxy-1,4-naphthoquinones we have considered the synthesis of water-soluble prodrugs. Only one naphthoquinone (1) of this type appears to have been reported and this apparently offered no advantages over the parent compound (2) when its antimalarial properties were evaluated in



(1) R^1 = O·CO·[CH_2]$_3$·N·(Et)$_2$. HCl, R^2 = [CH_2]$_8$·Hex^c

(2) R^1 = OH, R^2 = [CH_2]$_8$·Hex^c

(3) R^1 = O·CH_2·CH(OH)·CH_2OH, R^2 = Hex^c

(4) R^1 = OH, R^2 = Hex^c

infected rodents.[1] An alternative type of hydrophilic prodrug would be one containing a glyceride moiety. Glyceride prodrugs of aspirin have been reported to have marked advantages over the parent compound.[2] Accordingly we considered the synthesis of naphthoquinones such as compound (3) worthy of investigation. Since this compound is a vinylogous ester it was reasoned that under conditions of physiological pH, or possibly by enzymic reaction, it would readily revert to the hydroxy-compound (4). The latter compound is of interest because of its activity against the cattle parasite *Theileria parva*.[3]

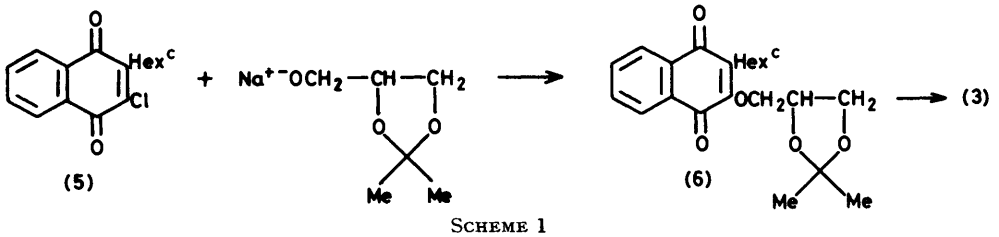
To date all attempts to obtain compound (3) have been unsuccessful. However, during the course of this investigation several novel facets of quinone chemistry were discovered and are reported herein.

Results and Discussion

Efforts to synthesise compound (3) were made using the route shown in Scheme 1. The sodium salt of 2,2-dimethyl-1,3-dioxan-4-ylmethanol reacted smoothly with 2-chloro-3-cyclohexyl-1,4-naphthoquinone (5) to give the desired quinone acetal (6) in good yield (86%).

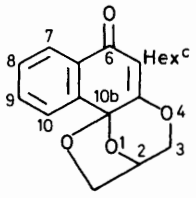
Treatment of this compound in refluxing methanolic hydrochloric acid for 15 min gave, as the sole product, crystalline material which appeared homogeneous by t.l.c. Elemental analysis gave a molecular formula $C_{19}H_{20}O_5$ which was confirmed by mass spectrometry (M^+, 312). The i.r. spectrum failed to reveal the presence of hydroxy-group absorption. Furthermore, although carbonyl absorption was seen at 1 640 cm^{-1}, a shoulder that is present at 1 670 cm^{-1} in the spectrum of the quinone acetal (6) was absent. The ^1H n.m.r. spectrum in deuteriochloroform showed signals due to aromatic protons at δ 8.1 (1 H) and 7.7 (3 H) and aliphatic protons (10 H) at δ 1—2 which were attributed to the five methylene groups of the cyclohexyl ring. The cyclohexyl methine signal was observed as a multiplet at δ 3.0 whilst complex absorption was seen at δ 4—5 integrating for five protons. On the basis of this evidence the compound was assigned structure (7), formation from compound (6) being rationalised as occurring by an intramolecular transacetalisation process.

Doubts as to the correctness of the structure assigned to compound (7) were raised when molecular models revealed the presence of severe ring strain. In contrast the isomeric acetal (8) with three 6-membered ether rings appeared strain free. In view of this the ^1H n.m.r.



Scheme 1

spectrum of the spiro-ether derived from compound (6) was re-examined. In the presence of the europium shift reagent $Eu(fod)_3$ two doublets were observed to move downfield from the aromatic signals. These were widely separated and in the ratio 3 : 1. It was concluded that each doublet arose from an aromatic proton *ortho* to a



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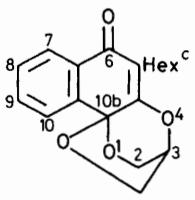
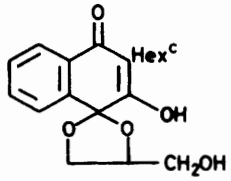


(8)

carbonyl moiety. Consequently it was deduced that the material resulting from acid treatment of compound (6) was, in fact, a mixture of the acetals (7) and (8) with one isomer [shown later to be (8)] predominating 3 : 1 over the other. Detailed examination of the mixture by t.l.c. failed to resolve the two components.

Treatment of the quinone acetal (6) with methanolic hydrochloric acid at 0 °C for 1.5 h gave rise to just one component of the mixture as judged by ^1H n.m.r. in the presence of $Eu(fod)_3$. The 90 MHz ^1H n.m.r. spectrum obtained after the addition of europium or praseodymium shift reagents showed the methylene and methine protons of the ether rings as complex signals compatible only with the ABCDE spin system of structure (7) and not with the AA'BB'C arrangement in structure (8). Further evidence for structure (7) was provided by base hydrolysis. Treatment of the material derived from



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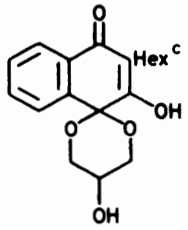
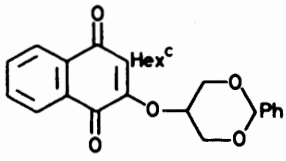


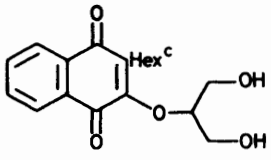
(10)

compound (6) with potassium hydroxide–methanol–water furnished an acetal which on the basis of n.m.r. evidence was concluded to be compound (9) and not the alternative compound (10) which would be formed from the isomer (8). The ^1H n.m.r. spectrum showed signals arising from two non-equivalent methylene groups as multiplets centred at δ 3.8 and 4.4. Irradiation at δ 4.9 ($OCHCH_2OH$ signal) resulted in both methylene signals collapsing to AB quartets. The low-field methylene signal showed additional splitting which was not due to coupling with the primary hydroxy-proton as D_2O addition failed to remove it. This small shift difference was consistent with the sample existing as a mixture of diastereoisomers.

In a study of the production of the isomers (7) and (8) from the quinone acetal (6), the latter was heated in refluxing methanolic hydrochloric acid for varying periods of time. The concentration of compound (7) in the reaction mixture (as measured by ^1H n.m.r.) decreased with time until after 16 h the product contained 5% of the isomer (7) and 95% of the isomer (8). Further heating failed to alter the composition of this mixture. In order to obtain the pure isomer (8) 1,3-benzylideneglycerol was allowed to react with the chloro-quinone (5) to give the quinone acetal (11). This, on treatment with methanolic hydrochloric acid for 65 h at room temperature, gave the desired compound in good yield (80%). This reaction was assumed to proceed *via* the diol (12).



(11)



(12)

The structure of the isomer (8) was confirmed by n.m.r.* In the presence of $Eu(fod)_3$ or $Pr(fod)_3$, three separate chemical shifts were seen for the ether methylene and methine protons as expected for the AA'BB'C system of the isomer (8). Further distinction between isomers (7) and (8) was provided by ^{13}C n.m.r. The methylene ether carbon atoms of the isomer (8) are equivalent and should appear as one signal. In contrast the corresponding atoms in the isomer (7) are non-equivalent and should give 2 resonances. Analysis of the ^{13}C n.m.r. spectrum of a 2 : 1 mixture of isomers (7) and (8) confirmed these predictions. The chemical shifts recorded for the methylene and methine ether carbons are shown in the Table. The assignments were confirmed by measurements of a proton coupled ^{13}C n.m.r. spectrum which showed triplet and doublet multiplicities for the methylene and methine carbons respectively.

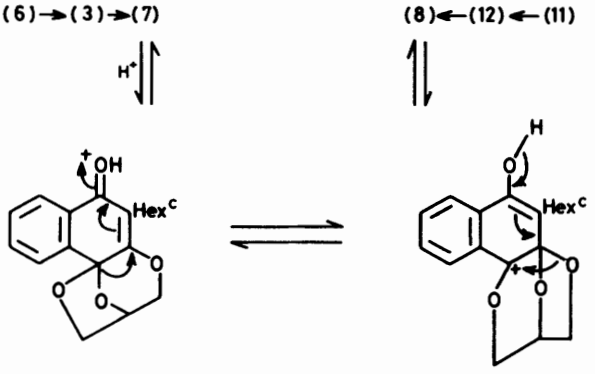
^{13}C N.m.r. chemical shifts in [$^2H_6$]dimethyl sulphoxide solution (p.p.m. from tetramethylsilane)

Isomer	CH_2	CH
(7)	67.7 66.6	74.0
(8)	72.0	68.7

As expected from molecular models, the isomer (8) was considerably more stable than the isomer (7) and no reaction occurred when it was subjected to the same hydrolytic conditions used to convert the isomer (7) into compound (9). When isomers (7) and (8) were heated in methanolic hydrochloric acid, both gave rise to mixtures of isomers (7) and (8). Thus, heating the isomer (7) for

* Since completion of this manuscript the structures of both isomers (7) and (8) have also been confirmed by *X*-ray crystallography. The structure of isomer (7) was determined by Dr. M. W. Extine, Ms. R. A. Meisner, and Dr. J. M. Troup of the Molecular Structure Corporation, College Station, Texas, USA. The structure of isomer (8) was determined by Professor A. McPhail of Duke University, Durham, North Carolina, USA.

15 min resulted in 22% of isomer (7) and 78% of isomer (8) whilst similar treatment of isomer (8) gave 7% of isomer (7) and 93% of isomer (8). In order to rationalise the interconversion of these acetals and their formation from compounds (6) and (11), the mechanism shown in Scheme 2 is proposed. The diols (3) and (12) were presumed to be intermediates and although they were never isolated, a t.l.c. study of the conversion of the quinone acetal (6) into the isomer (7) did show the presence of polar material which conceivably could have been the desired compound (3).



SCHEME 2

Attempts to synthesise the isomer (8) by reaction of glycerol with 2-hydroxy-3-cyclohexyl-1,4-naphthoquinone (4), using the standard conditions for acetalisation of carbonyl groups (acid catalysis, anhydrous copper sulphate) were unsuccessful. Similarly, efforts to obtain compound (9) by transacetalisation of compound (4) with 2,2-dimethyl-1,3-dioxan-4-ylmethanol failed. These results are in accord with the fact that direct acetalisation of quinone carbonyl groups by alcohols does not appear to be a standard method reported in the literature. Instead, quinone acetals are prepared *via* oxidative processes such as the anodic oxidation of hydroquinone ethers.[4] In view of this, the work reported above illustrating quinone acetalisation by a direct intramolecular process is of some interest, particularly since it allows selective protection of one of the quinone carbonyl functions. This may be of value in further studies on the chemistry of the hydroxynaphthoquinones, as the acetal (9) can readily be converted into 2-cyclohexyl-3-hydroxy-1,4-naphthoquinone by treatment with acid.

EXPERIMENTAL

Melting points, uncorrected, were recorded using an Electrothermal capillary tube melting point apparatus. I.r. spectra were measured as potassium bromide discs (solids) or between sodium chloride plates (oils), on a Perkin-Elmer 157G spectrometer. N.m.r. spectra were determined using Bruker HFX-90 or Bruker WP-80 Fourier transform instruments for solutions in deuteriochloroform with tetramethylsilane as internal standard unless otherwise stated. Mass spectra (e.i.) were obtained with an A.E.I. MS 902 spectrometer operating at 70 eV. T.l.c. was carried out with Merck GF_{254} silica gel plates using toluene–ethyl acetate solvent systems.

2-*Cyclohexyl*-3-(2,2-*dimethyl*-1,3-*dioxolan*-4-*ylmethoxy*)-1,4-*naphthoquinone* (6).—Sodium hydride (50% dispersion in mineral oil; 1.1 g, 22 mmol) was added in portions with vigorous stirring to 2,2-dimethyl-1,3-dioxan-4-ylmethanol * (20 ml) under dry nitrogen. After the initial exothermic reaction had subsided the resulting solution was cooled to room temperature and 2-chloro-3-cyclohexyl-1,4-naphthoquinone [3] (5) (5.5 g, 20 mmol) was added. The reaction mixture was stirred for 1.5 h at room temperature, diluted with toluene (100 ml), and acidified with glacial acetic acid (1 ml). After it had been washed with water (4 × 50 ml) and dried ($MgSO_4$) the toluene solution was evaporated to give crude product (8.34 g). This was purified by chromatography on neutral alumina (100 g), the required material being eluted pure with ethyl acetate as a pale yellow *oil* (6.95 g, 94%) (Found: C, 71.45; H, 6.95. $C_{22}H_{26}O_5$ requires C, 71.33; H, 7.08); δ 1.40 (3 H, s, Me), 1.42 (3 H, s, Me), 3.15 (1 H, m, CH of cyclohexyl), 3.9—4.7 (5 H, m, OCH_2CH-CH_2O), 7.80 (2 H, m, ArH), and 8.1 (2 H, m, ArH); $\nu_{max.}$ 1 670 and 1 655 cm^{-1}.

2-Cyclohexyl-3-(*cis*-2,2-phenyl-1,3-dioxan-5-yloxy)-1,4-naphthoquinone (11).—Sodium hydride (50% dispersion in mineral oil; 1.3 g, 27 mmol) was added to dry dimethylformamide (10 ml) under nitrogen and the resulting suspension cooled to 0 °C. A solution of *cis*-1,3-*O*-benzylideneglycerol [5,6] (3.96 g, 22 mol) in dimethylformamide (10 ml) was then added dropwise during 10 min with vigorous stirring. After a further 10 min, 2-chloro-3-cyclohexyl-1,4-naphthoquinone (5) (5.5 g, 20 mmol) was added; the reaction mixture was then stirred at room temperature for 30 min, diluted with toluene (150 ml), and acidified with glacial acetic acid (2 ml). After being washed with water (4 × 100 ml), the toluene solution was dried ($MgSO_4$) and evaporated to give a dark red oil (7.21 g). This was crystallised from toluene–light petroleum (b.p. 60—80 °C) to give the required product as yellow *crystals* (4.08 g, 49%), m.p. 116—117 °C (Found: C, 74.4; H, 6.25. $C_{26}H_{26}O_5$ requires C, 74.62; H, 6.26%); δ 3.41 (1 H, m, CH of cyclohexyl), 4.31 (4 H, m, 2 × CH_2O), 4.96 [1 H, quintet, OCH-$(CH_2)_2$], and 5.6 (1 H, s, CHO_2); $\nu_{max.}$ 1 670 and 1 655 cm^{-1}.

5-*Cyclohexyl*-10b,2-*epoxymethano*-2,3-*dihydronaphtho*-[1,2-b]*dioxin*-6(10bH)-*one* (7).—2-Cyclohexyl-3-(2,2-dimethyl-1,3-dioxolan-4-ylmethoxy)-1,4-naphthoquinone (6) (4.0 g, 10.8 mmol) was dissolved in methanol (80 ml) and the resulting solution was cooled to 0 °C; concentrated hydrochloric acid (16 ml) was then added with vigorous stirring. After 1.5 h at 0 °C, the reaction mixture was filtered and the solid obtained was washed with ice-cold methanol and then dried to give the desired product as colourless *crystals* (2.08 g, 62%), m.p. 182—183 °C, raised by recrystallisation from methanol to 186—188 °C (Found: C, 73.35; H, 6.5. $C_{19}H_{20}O_4$ requires C, 73.07; H, 6.41%); δ 1.2—2.1 (10 H, m, 5 × CH_2 of cyclohexyl), 3.0 (1 H, m, CH of cyclohexyl), 4.2—4.5 (4 H, m, 2 × CH_2O), 4.9 (1 H, m, CHO), 7.4—7.7 (3 H, m, ArH), and 8.1 (1 H, m, ArH); $\nu_{max.}$ 1 645 cm^{-1}.

5-*Cyclohexyl*-10b,3-*epoxymethano*-2,3-*dihydronaphtho*-[1,2-b]*dioxin*-6-(10bH)-*one* (8).—2-Cyclohexyl-3-(*cis*-2-phenyl-1,3-dioxan-5-yloxy)-1,4-naphthoquinone (11) (3.0 g, 7.2 mmol) was dissolved in warm methanol (180 ml) and the resulting solution cooled to room temperature and concentrated hydrochloric acid (12 ml) added with vigorous

* Solketal, Aldrich Chemical Co. Inc.

stirring. The resulting mixture was stirred at room temperature for 3 d and then cooled in ice; the product was filtered off, washed with ice cold methanol, and dried to give pale yellow crystals (1.79 g, 80%), m.p. 197—199 °C. Recrystallisation from methanol gave *crystals*, m.p. 210—213 °C (Found: 72.8; H, 6.2. $C_{19}H_{20}O_4$ requires C, 73.07; H, 6.41%); δ 1.2—2.2 (10 H, m, 5 × CH_2 of cyclohexyl), 2.99 (H, m, CH of cyclohexyl), 4.37 (4 H, m, 2 × CH_2O), 4.70 (1 H, m, CHO), 7.4—7.8 (3 H, m, ArH), and 8.1 (1 H, m, ArH); $\nu_{max.}$ 1 640 cm^{-1}.

Conversion of the Quinone (6) *into the Isomers* (7) *and* (8).—(*a*) Compound (6) (50 mg) was heated in refluxing methanol (1 ml) with concentrated hydrochloric acid (0.2 ml) for 15 min. The solution was cooled in ice and the precipitated solid filtered off, washed with ice-cold methanol, and dried to give pale yellow crystals (20 mg), m.p. 176—180 °C (softening at 151 °C) which were a mixture of the isomer (7) (26%) and the isomer (8) (74%) (as determined by ^1H n.m.r. in the presence of $Eu(fod)_3$.

(*b*) Treatment of compound (6) (50 mg) as above for 2 h at reflux temperature gave a mixture (30 mg), m.p. 186—190 °C (softening at 175 °C), of the isomer (7) (15%) and the isomer (8) (85%).

(*c*) Treatment of compound (6) (50 mg) as above for 16 h at reflux temperature gave a mixture (20 mg), m.p. 195—198 °C of the isomer (7) (5%) and the isomer (8) (95%).

Interconversion of the Isomers (7) *and* (8).—(*a*) The isomer (7) (50 mg) was heated in refluxing methanol (1 ml) with concentrated hydrochloric acid (0.2 ml) for 15 min. After work-up as described above the resulting product (25 mg), m.p. 180—185 °C, was shown to consist of the isomer (7) (22%) and the isomer (8) (78%).

(*b*) Treatment of the isomer (8) (50 mg) as above gave a product (30 mg), m.p. 195—198 °C, containing the isomer (7) (7%) and the isomer (8) (93%).

3-Cyclohexyl-4′,5′-dihydro-2-hydroxy-4′-hydroxymethylnaphthalene-1-spiro-2′-dioxol-4-one (9).—Compound (7) (200 mg, 0.6 mmol) and potassium hydroxide (200 mg) were heated at reflux in methanol (8 ml)–water (1 ml) for 2 h. The deep red solution was cooled in ice and acidified with glacial acetic acid (0.4 ml). The precipitated yellow solid was filtered off, washed with water, and dried to give compound (9) (180 mg, 84%). Crystallisation of a small sample from methanol gave cream coloured *crystals*, m.p. 166—168 °C (Found: C, 68.9; H, 6.8. $C_{19}H_{22}O_5$ requires C, 69.07; H, 6.71%); δ 2.91 (1 H, m, CH of cyclohexyl), 3.83 (2 H, m, CH_2O), 4.35 (2 H, m, CH_2OH), 4.96 (1 H, m, OCH), 7.58 (3 H, m, ArH), and 7.89 (1 H, m, ArH); $\nu_{max.}$ 3 350 and 1 625 cm^{-1}.

Conversion of the Acetal (9) *into 2-Cyclohexyl-3-hydroxy-1,4-naphthoquinone* (4).—Concentrated hydrochloric acid (0.1 ml) was added to compound (9) (20 mg) in methanol (0.6 ml) and the resulting solution heated at reflux for 30 min. When the mixture was cooled in ice, bright yellow crystals were deposited (10 mg, 65%), m.p. 130—131 °C, which were identical with an authentic sample of 2-cyclohexyl-3-hydroxy-1,4-naphthoquinone.[7]

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