Applications of High-potential Quinones. Part X.[1] Reactions of 3,4-Dihydrocoumarin Derivatives

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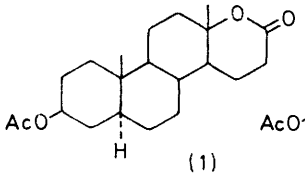
Ring opening is preferred to dehydrogenation when 3,4-dihydrocoumarins react with *ortho*- or *para*-chloranil or with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in alcoholic solvents, the quinones acting as Lewis acid catalysts. The alcoholysis products react further with DDQ to give coupled adducts.

SATURATED LACTONES are dehydrogenated less readily than cyclic ketones by DDQ, probably owing to less favourable enolization of the lactone carbonyl group.[2] Typical conditions for conversion of the steroidal



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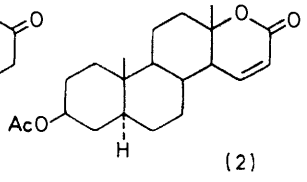

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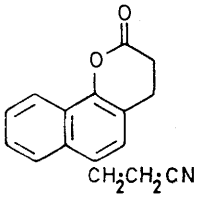

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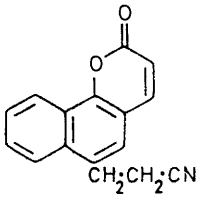

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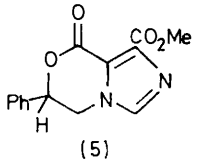

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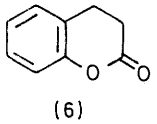

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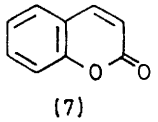

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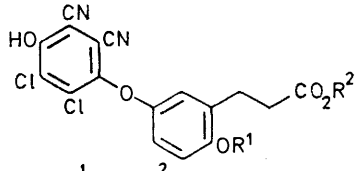
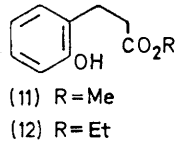
lactone (1) into its 15,16-didehydro-derivative (2) involve prolonged reaction in refluxing dioxan with an excess of the quinone, and only a 25% yield is obtained.[3] The lactone (3), which possesses benzylic hydrogen atoms, is dehydrogenated to the coumarin (4) by DDQ in 70% yield after less prolonged reaction,[4] although the heterocyclic lactone (5) appears to be inert to DDQ, in spite of having a tertiary benzylic hydrogen atom.[5] Under similar conditions dihydrocoumarin (6) showed 56% conversion into coumarin (7), although treatment with an excess of the quinone did not lead to complete dehydrogenation.

When DDQ reacted with dihydrocoumarin (6) in methanol, a different type of reaction occurred, with complete consumption of starting materials in a few hours at room temperature. However, no coumarin (7) was detected in the product mixture by t.l.c., and much smaller amounts of dichlorodicyanohydroquinone were formed. The major product, obtained in high yield, was the coupled, ring-opened ester (8). The structure of this compound was evident from its analytical and spectral data, and those of the derived monoacetate (9). In particular, the n.m.r. spectra showed only three protons in the aromatic region. Since it is known [6] that *ortho*-substituted phenols give



(8) R^1 = H, R^2 = Me
(9) R^1 = Ac, R^2 = Me
(10) R^1 = H, R^2 = Et



(11) R = Me
(12) R = Et

this type of product with DDQ, it was evident that ring opening to give the methyl β-arylpropionate (11) was the initial reaction. This was confirmed by repeating

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the reaction with less than 1 equiv. of DDQ; this gave the ester (11) together with the adduct (8). The reaction followed a similar course in ethanol, giving the ring-opened ester (12) and the derived adduct (10).

In these reactions the quinone appeared to function as a Lewis acid catalyst, and, in agreement with this, small proportions of DDQ were effective in promoting ring opening in primary and secondary alcohols (Table 1),

TABLE 1

Alcoholyses of 3,4-dihydrocoumarin catalysed by DDQ *

Alcohol	β-(2-Hydroxyphenyl)-propionate	Yield (%)	R_F † A	R_F † B
MeOH	Methyl	57	0.62	0.20
EtOH	Ethyl	46	0.65	0.22
Pr^nOH	Propyl	44	0.68	0.24
Pr^iOH	Isopropyl	48	0.68	0.23

* Molar ratio 15 : 1. † A, $CHCl_3$–Et_2O (7 : 3); B, $CHCl_3$–C_6H_6 (1 : 1).

leading to the corresponding phenolic esters. Although a similar reaction seemed to occur in t-butyl alcohol, neither the expected adduct nor the ring-opened ester could be isolated from the complex product mixture. The photoinduced alcoholysis of 3,4-dihydrocoumarin, which involves a keten intermediate,[7] has been carried out in a variety of alcohols,[8] but no alcoholysis occurs in t-butyl alcohol.

The quinone may function by π-complex formation with the aromatic ring of dihydrocoumarin. This should decrease the availability of the more polarizable of the ether oxygen lone pairs [9] for delocalization into the carbonyl group, thereby facilitating ring opening of the lactone by nucleophilic attack of the alcohol upon the carbonyl group. Co-ordination of DDQ with an oxygen atom of the lactone system appears less likely. Quinones of higher potential were found to be better catalysts for the reactions. Comparisons of the efficiency

TABLE 2

Rates of quinone-catalysed methanolysis of 3,4-dihydrocoumarin

(i) In methanol

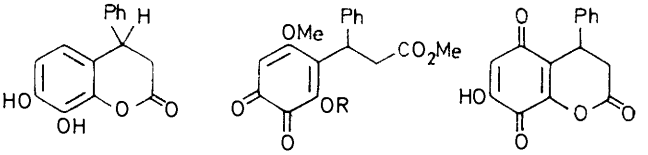
t/hr	% Reaction DDQ	% Reaction *o*-Chloranil	% Reaction Uncatalysed
0.5	52	60	—
1.0	60	92	20
2.0	86	91	19
4.0	99	92	20

(ii) In methanol–toluene (2 : 1)

t/h	% Reaction DDQ	% Reaction *p*-Chloranil
1.0	36	32
3.0	62	41
6.0	74	62

of *para*-chloranil, *ortho*-chloranil, and DDQ for inducing alcoholysis were obtained by n.m.r. spectroscopic estimation of the amounts of methyl hydroxy-ester formed. The results (Table 2) show *ortho*-chloranil to be marginally superior to DDQ, with *para*-chloranil the least effective. There is the alternative possibility that liberation of traces of acid by displacement of one of the electronegative substituents of DDQ by the alcohol could lead to normal acid catalysis of the alcoholysis of the dihydrocoumarin. No reaction was observed when coumarin or γ-valerolactone was treated with DDQ in methanol.

The behaviour of the substituted dihydrocoumarin (13) was also studied, as the benzylic hydrogen atom in this compound is highly activated. Ring opening of the lactone also occurred in this case, a complex mixture being obtained upon oxidation with DDQ in methanol. The major product isolated by t.l.c. was a quinone having two methoxy-groups. Its n.m.r. spectrum also



(13) (14) R = H (15) R = Ac (16)

showed a sharp one-proton singlet in the vinylic region, and structure (14) is considered the most likely, since this signal showed a downfield shift of only 0.07 p.p.m. in the derived monoacetate (15). A downfield shift of approximately three times this magnitude is expected for the isomeric structure.[10] A reaction mechanism involving (i) oxidation to the *ortho*-benzoquinone, (ii) DDQ-catalysed ring-opening, (iii) addition of methanol to the *ortho*-quinone, and (iv) re-oxidation is envisaged for the formation of the quinone (14), although the sequence in which these steps occur is a matter for conjecture. Several other more polar products, probably coupled adducts, were formed in the reaction, but attempts to isolate and purify them failed. Formation of coupled adducts was also suspected when the reaction was carried out in dioxan, on the basis of the absence of precipitated hydroquinone, but again no pure products could be obtained. Oxidation of the phenol (13) with potassium nitrosodisulphonate proceeded normally without attack at the benzylic position to give the *para*-benzoquinone (16). This quinone was rather unstable, and gave a complex mixture of products upon acetylation, perhaps owing to tautomerization. Use of sodium periodate in aqueous acetone gave an intractable red product which appeared to be dimeric from its mass spectrum.

The absence of benzylic oxidation of the dihydrocoumarin (13) in the transformations described in this paper is probably due to the ease of the competing reactions rather than to steric hindrance to attack by high-potential quinones, since the tetrakis-(3,4-dimethoxyphenyl)ethane (17), which possesses similarly

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activated tertiary hydrogen atoms, gave tetrakis-(3,4-dimethoxyphenyl)ethene (18) with DDQ in dioxan.

$Ar_2CH{\cdot}CHAr$ (17) $\qquad$ $Ar_2C{=}CAr_2$ (18)

Ar = 3,4-$(OMe)_2C_6H_4$

Dehydrogenation was slow at room temperature, but proceeded to completion in the refluxing solvent. The presence of electron-releasing substituents in the 4- and 4′-positions of bibenzyl leads to good yields of the corresponding *trans*-stilbenes, whereas incomplete hydrogen transfer with DDQ is observed in the absence of activating groups.[2] Tetraphenylethane is not dehydrogenated by high-potential quinones.[2]

EXPERIMENTAL

T.l.c. was carried out on silica gel (Merck GF254) with location by u.v. illumination or iodination. G.l.c. was conducted on 2 m × 3 mm (o.d.) stainless steel columns packed with 2.5% silicone gum rubber E-301 on AW-DMCS Chromosorb W (80—100 mesh) at 140 °C with a nitrogen flow rate of 23 ml min^{-1} on a Perkin-Elmer F-11 instrument. Quoted retention times are relative to dihydrocoumarin (t_R 1.0). For other general directions see ref. 10.

Dehydrogenation of 3,4-*Dihydrocoumarin*.—A solution of dihydrocoumarin (300 mg) and DDQ (463 mg, 1.1 equiv.) in dioxan (6.0 ml) was heated under reflux for 180 h. The precipitated hydroquinone (320 mg, 69%) was collected, and the filtrate was concentrated *in vacuo*. The residual brown oil was dissolved in ethyl acetate and filtered through neutral alumina (Woelm, activity 1; 6.0 g). Evaporation of the eluate gave a pale yellow gum (270 mg), which was shown by g.l.c. analysis to consist of coumarin (t_R 1.96) and dihydrocoumarin in the ratio 56 : 43.

The reaction was repeated with dihydrocoumarin (200 mg) and DDQ (616 mg, 2 equiv.) in dioxan (3.0 ml) and a reflux period of 262 h. Dichlorodicyanohydroquinone (391 mg, 63%) was obtained, together with a crude product (185 mg) shown to consist of coumarin and dihydrocoumarin in ratio 59 : 40 by g.l.c. analysis.

Alcoholyses of 3,4-*Dihydrocoumarin*.—(a) *Catalytic amount of DDQ*. Reactions (Table 1) were carried out as follows. To a solution of 3,4-dihydrocoumarin (200 mg, 1.35 mmol) in the appropriate alcohol (6.0 ml) was added DDQ (20 mg, 0.09 mmol), and the resulting orange solution was left at ambient temperature for 8 h, after which only a single component was detectable by t.l.c. (benzene–hexane, 4 : 1). DDQ and related compounds remained at the origin in this system. Preparative t.l.c. in the same system yielded the products listed in Table 1. These were identical with authentic samples obtained by esterification of 3-(2-hydroxyphenyl)propanoic acid in the presence of sulphuric acid as follows: methyl ester (92%), m.p. 44—46° (from light petroleum) (lit.,[8] 45.6—46°), τ 7.17 (m, $CH_2{\cdot}CH_2$), 6.27 (s, CO_2Me), and 2.65—3.25 (m, ArH); ethyl ester (93%), m.p. 33.5—35° (from light petroleum) (lit.,[8] 34—35°), τ 8.77 (t, *J* 7 Hz, Me), 8.28 (m, $CH_2{\cdot}CH_2$), 5.81 (q, *J* 7 Hz, CH_2), and 2.62—3.23 (m, ArH); *propyl ester* (80%), b.p. 82—83° at 0.01 mmHg (Found: C, 68.8; H, 7.5. $C_{12}H_{16}O_3$ requires C, 69.2; H, 7.7%), $\lambda_{max.}$ 273 nm (ε 3 800), $\nu_{max.}$ 3 370, 1 730, 1 698, 1 610, and 1 595 cm^{-1}, τ 9.05 (t, *J* 7 Hz, Me), 8.28 (m, CH_2), 7.12 (m, $CH_2{\cdot}CH_2$), 5.88 (m, CH_2), and 2.45—3.25 (m, ArH); isopropyl ester (78%), b.p. 108—110° at 0.05 mmHg (lit.,[8] 119—122° at 0.5 mmHg), τ 8.78 (d, *J* 6.5 Hz, Me_2), 7.17 (m, $CH_2{\cdot}CH_2$), 4.93 (q, *J* 6.5 Hz, CH), and 2.69—3.26 (m, ArH). Acetylation of the methyl ester (Ac_2O–C_5H_5N) gave *methyl* 3-(2-*acetoxyphenyl*)*propanoate* (91%) as an oil, b.p. 82° at 0.02 mmHg (Found: C, 64.8; H, 6.3. $C_{12}H_{14}O_4$ requires C, 64.8; H, 6.3%), R_F ($CHCl_3$–Et_2O, 7 : 3) 0.69, ($CHCl_3$–C_6H_6, 1 : 1) 0.40, $\lambda_{max.}$ 268 nm (ε 3 700), $\nu_{max.}$ 1 610 and 1 587 cm^{-1}, τ 7.67 (s, OAc), 7.23 (m, $CH_2{\cdot}CH_2$), 6.30 (s, CO_2Me), and 2.62—3.05 (m, ArH).

(b) *Equimolar proportion of DDQ*. A solution of DDQ (3.1 g) in methanol (20 ml) was added dropwise during 10 min to a stirred solution of dihydrocoumarin (2.0 g) in methanol (20 ml). The solution was stored for 18 h in the dark at 20 °C. The resulting red solution was evaporated to a red oil which partially dissolved upon addition of benzene (50 ml). The insoluble hydroquinone (0.7 g, 22%) was collected and washed with benzene. After concentration and refrigeration the benzene solution afforded *methyl* 3-[2-(2,3-*dichloro*-5,6-*dicyano*-4-*hydroxyphenoxy*)-5-*hydroxy*]*phenylpropanoate* (8) (3.1 g, 56%) as needles, m.p. 176—181° (decomp.), raised by two recrystallisations from aqueous methanol to 181—183° (decomp.) (Found: C, 50.5; H, 3.6; N, 6.7%; M^+, 406.0120. $C_{18}H_{12}Cl_2N_2O_5,H_2O$ requires C, 51.0; H, 3.3; N, 6.6%; *M* for $^{35}Cl_2$, 406.0123), $\lambda_{max.}$ 252 and 387 nm (ε 33 600 and 9 400), $\nu_{max.}$ 3 470, 3 360, 2 240, 1 705, 1 270, 1 190, 1 080, 1 020, 950, 895, and 805 cm^{-1}, τ (CD_3OD) 7.26 (m, $CH_2{\cdot}CH_2$), 6.38 (s, CO_2Me), and 3.32 (m, ArH), *m/e* 408 (2%), 406 (4), 376 (53), 375 (14), 374 (100), 348 (22), 347 (18), 346 (45), 345 (16), 332 (11), 135 (11), and 118 (10). The compound slowly darkened on exposure to the atmosphere in diffuse sunlight. Overnight acetylation of the adduct (152 mg) in pyridine (5 ml) and acetic anhydride (2 ml) gave the *monoacetate* (9) (122 mg, 73%), m.p. 56—59° (from methanol) (Found: M^+, 448.0229. $C_{20}H_{14}{}^{35}Cl_2N_2O_6$ requires *M*, 448.0228), τ ($CDCl_3$) 7.68 (s, OAc), 7.28 (m, $CH_2{\cdot}CH_2$), 6.33 (s, CO_2Me), 3.18 (s, 6′-ArH), and 3.11 (q, *J* 8 Hz, 3′- and 4′-ArH), *m/e* 450 (0.3%), 448 (0.5), 408 (10), 406 (20), 376 (32), 375 (13), 374 (53), and 346 (9).

Repetition of the reaction in ethanol with 2.2 g (0.7 equiv.) of DDQ gave the hydroquinone (0.05 g) and the *ethyl ester* (10) (2.5 g, 61%), as needles, m.p. 176—179° (from aqueous ethanol) (Found: M^+, 420.0282. $C_{19}H_{14}{}^{35}Cl_2N_2O_5$ requires *M*, 420.0279), $\lambda_{max.}$ 254 and 390 nm (ε 30 500 and 8 700), $\nu_{max.}$ 3 440, 3 200, 2 240, 1 710, 1 270, 1 230, 1 170, 1 080, 1 045, 1 015, 920, 895, 855, 820, and 790 cm^{-1}, τ (CD_3OD) 8.80 (t, *J* 6 Hz, Me), 7.30 (m, $CH_2{\cdot}CH_2$), 5.93 (q, *J* 6 Hz, CH_2), and 3.33 (m, ArH), *m/e* 422 (5%), 420 (8), 376 (37), 375 (16), 374 (71), 348 (20), 347 (18), 346 (33), and 345 (11).

Rate studies. Data (Table 2) for the rates of ring opening catalysed by various quinones were obtained by estimating the amount of methyl ester produced by n.m.r. spectroscopy. Lactone–ester mixtures were separated from the quinones by t.l.c. (hexane–benzene, 1 : 1) and the percentage of the total integral contributed by the ester methyl protons was determined.

Attempted Methanolysis of γ-*Valerolactone*.—A solution of the lactone (100 mg) and DDQ (228 mg, 1 equiv.) in methanol (3 ml) was stored at ambient temperature for 3 days. The residue left after evaporation was taken up in ethyl acetate and filtered through neutral alumina (12 g).

Evaporation of the eluate yielded unchanged γ-valerolactone (91 mg).

Oxidation of 3,4-Dihydro-7,8-dihydroxy-4-phenylcoumarin.[11]—(a) *With DDQ.* Solutions of the dihydrocoumarin (13) (256 mg) in methanol (10 ml) and DDQ (456 mg) in methanol (10 ml) were mixed. After 60 h at ambient temperature the methanol was removed *in vacuo* and dioxan (15 ml) was added to the residue. Insoluble hydroquinone (381 mg, 83%) was collected and washed with dioxan (5 ml). The dioxan solution was evaporated and the residue (320 mg) was separated into five zones on t.l.c. (benzene–ethyl acetate, 7 : 3). The violet zone (R_F 0.96) was separated to give *methyl 3-(3-hydroxy-5-methoxy-1,2-benzoquinone-4-yl)-3-phenylpropionate* (14) as an orange oil (56 mg, 18%) (Found: M^+, 316.0944; $M - CH_3OH$, 284.0687. $C_{17}H_{16}O_6$ requires 316.0946. $C_{16}H_{12}O_5$ requires 284.0684), $\lambda_{max.}$ 399 nm (ε 950), $\nu_{max.}$ 3 310, 1 730, 1 675, 1 630, 1 610, 1 090, 845, and 700 cm^{-1}, τ ($CDCl_3$) 6.85 (m, CH_2), 6.40 (s, OMe), 6.24 (s, CO_2Me), 5.22 (m, CH), 4.19 (s, 6-H), and 2.76 (m, ArH), *m/e* 316 (5%), 285 (22), 284 (100), 283 (20), 256 (25), 243 (18), 241 (28), 213 (10), and 115 (25). Acetylation (C_5H_5N–Ac_2O) gave the *acetate* (15) as an orange gum (95%) (Found: $M - C_2H_2O$, 316.0944. $C_{17}H_{16}O_6$ requires 316.0946), $\nu_{max.}$ 1 735, 1 680, 1 630, and 1 615 cm^{-1}, τ 7.72 (s, OAc), 6.80 (m, CH_2), 6.38 (s, OMe), 6.22 (s, CO_2Me), 5.20 (m, CH), 4.12 (s, 6-H), and 2.76 (m, ArH), *m/e* 360 (1.5%), 358 (1), 356 (4.5), 316 (10), 315 (14), 314 (100), 286 (32), 285 (17), 284 (60), 283 (20), 282 (25), 267 (20), 256 (22), 243 (32), 213 (4), 122 (25), and 105 (25).

(b) *With Fremy's salt.*[12] A solution of the dihydrocoumarin (200 mg) in acetone (50 ml) was treated with aqueous 10% acetic acid (80 ml) followed by potassium nitrosodisulphonate (500 mg). The mixture was shaken for 15 min, a further 500 mg of oxidant was added, and shaking was continued for 45 min. The mixture was extracted with chloroform and the extract was dried (Na_2SO_4) and evaporated to give *3,4-dihydro-7-hydroxy-4-phenylcoumarin-5,8-quinone* (16) as a brick red solid (105 mg, 50%) of indefinite m.p. (Found: M^+, 270.0529. $C_{15}H_{10}O_5$ requires M, 270.0528), $\lambda_{max.}$ 245 and 288 nm (ε 15 100 and 38 900), $\nu_{max.}$ 3 360, 2 920, 1 760, 1 675, 1 650, 1 610, 1 250, 1 180, 1 120, 1 025, 790, and 710 cm^{-1}, τ [$(CD_3)_2CO$] 7.10 (q, *J* 16 and 2 Hz, H of CH_2), 6.65 (q, *J* 16 and 2 Hz, H of CH_2), 5.69 (dd, *J* 7 and 2 Hz, CH) 4.04 (s, olefinic H), and 2.73 (m, ArH), *m/e* 270 (100%), 243 (32), 229 (13), 214 (11), 213 (25), 200 (13), 199 (25), 155 (10), 131 (11), 115 (18), 104 (13), and 103 (10). Acetylation (Ac_2O–C_5H_5N) gave a brown solid which showed several components on t.l.c.

Tetrakis-(3,4-dimethoxyphenyl)ethene.[13]—A solution of 1,1,2,2-tetrakis-(3,4-dimethoxyphenyl)ethane (190 mg) and DDQ (85 mg) in dioxan (6 ml) was boiled under reflux for 22 h. The usual work-up gave the hydroquinone (84 mg, 97%) and the *ethene* (172 mg, 91%) as pale green needles, m.p. 173—174° (from ethanol) (Found: C, 71.2; H, 6.3. $C_{34}H_{36}O_8$ requires C, 71.3; H, 6.4%), $\lambda_{max.}$ 220, 262, 295, and 344 nm (ε 31 900, 19 400, 12 800, and 9 800), τ 6.41 (s, OMe), 6.13 (s, OMe), and 3.30br (s, ArH) (ratio 1 : 1 : 1), highly fluorescent in solution and on t.l.c. plates under u.v. light.

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