Oxidation of Aromatic Substrates. Part II.[1] The Action of Ruthenium Tetraoxide on Some Derivatives of Naphthalene and its Monoaza-analogues

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Although benzene and pyridine undergo rapid reactions with ruthenium tetraoxide, the products of which have not been characterised, naphthalene derivatives and their monoaza-analogues afford phthalic or pyridine-2,3-dicarboxylic acids by selective ring cleavage. A procedure which obviates losses during work-up in the presence of surface-active ruthenium dioxide is described. The analogy with ozonolysis provides a guide in predicting the behaviour of substrates on treatment with ruthenium tetraoxide.

WHEN we began our work Rylander [2] had reported reactions of 1-nitronaphthalene and tetralin with ruthenium tetraoxide but no products were isolated. The only other report of the action of this vigorous

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electrophilic reagent on a polynuclear aromatic compound then available [3] described the oxidation of pyrene as non-specific. In view of these results the aim of our initial study [4] was to establish whether the naphthalene nucleus would undergo total or selective cleavage.

The effect of even a weakly electron-donating group on the ease of oxidation of an aromatic ring is well illustrated by the contrasting behaviour of oestradiol diacetate, which largely undergoes α-oxygenation, and its ring-A methylated homologue, in which case destruction of the aromatic system is predominant.[5] The naphthols therefore provide suitable models for establishing if there exists a tendency for random degradation, through interaction of the hydroxy-group with the more extensively delocalised system, or whether selective attack on the substituted ring is preferred.

Products of oxidation of naphthalenes and monoaza-naphthalenes by ruthenium tetraoxide

Substrate	Method and reaction time	Product	% Yield as diester
Naphthalene			
1-OH	A, 30 min	Phthalate [b,c]	41
	B, short [a]		50
	C, short [a]		55
1-OAc	B, 35 min	Phthalate [b]	51
2-OH	C, 25 min	Phthalate [b]	56
1-OMe	B, 2·5 h	Phthalate [b]	50
5-OMe, 1-OH	C, 25 min	3-OMe-phthalate [b]	50
Quinoline	C, 1 h	*o*-$C_5H_3N(CO_2Me)_2$ [d] (60% recovery)	45
Quinolin-8-ol	C, short [a]	*o*-$C_5H_3N(CO_2Me)_2$ [d]	95
Isoquinoline	C, 1 h	Phthalate [c,e]	58

[a] <30 min. [b] Diethyl ester. [c] Characterised by b.p. and comparison of i.r. and u.v. spectra and g.l.c. behaviour with a reference sample. [d] Dimethyl pyridine-2,3-dicarboxylate. [e] Dimethyl ester.

To obtain a direct comparison between the single phase aqueous acetone–periodate procedure (Method A of Experimental section) and the two-phase periodate and hypochlorite procedures (B and C) the dicarboxylic acids formed were isolated and characterised as their diethyl or dimethyl esters. If we allow for loss during diesterification the tabulated results show that good yields of phthalic acids may be obtained from naphthols.

The results obtained [4] for the naphthols are similar to those recently reported [6] by Spitzer and Lee. These authors studied a range of substituted naphthalenes and established a tendency for mixtures of both possible phthalic acids to be formed when the fused rings have comparable nucleophilic character. In this work long reaction times were necessary for the less reactive substrates as only very small amounts of ruthenium trichloride were used to generate the primary oxidant. Reaction times can be greatly reduced by using larger amounts of the primary oxidant provided that the aqueous hypochlorite or periodate used to regenerate it from ruthenium dioxide is in contact with an organic phase, typically carbon tetrachloride. In the presence of an excess of secondary oxidant all the ruthenium will attain the tetraoxide level at the end of the reaction, but as this compound is considerably more soluble in the organic phase ($CCl_4 : H_2O$ as 58 : 1) separation of this layer *before* destroying the tetraoxide ensures that contact between products and precipitated ruthenium dioxide is kept to a minimum. The dioxide adsorbs free carboxylic acids so strongly that extraction with hot aqueous sodium hydroxide is necessary if they are to be recovered in good yield; failure to appreciate this may partly account for low yields in carboxylic acid synthesis by this method. For these reasons a two-phase procedure is preferred. Another feature affecting acid yields is the incidence of attack at α-positions seen in oestradiol diacetate.[5] Although no evidence of this form of attack was found [6] for alkylnaphthalenes only small proportions of these starting materials were accounted for. Whereas *O*-acetylation served to protect the aromatic ring of oestradiol, we found that 1-naphthyl acetate was rapidly oxidised to give a yield of phthalic acid similar to that obtained from 1-naphthol. This reaction was carried out with periodate in the aqueous phase (pH 6·3) to reduce solvolysis to a minimum.

Spitzer and Lee's results [6] show that the reactivity of the ring bearing a methoxy-group is greatly enhanced, although some methoxyphthalic acid was isolated on oxidation of 2-methoxynaphthalene. An experiment with 5-methoxy-1-naphthol is significant in that total fragmentation was avoided and 3-methoxyphthalic acid was obtained in good yield; this demonstrates the controlling influence of the free phenol in competition with another strong donor group. The preferential destruction of the phenolic ring was favoured by working with sodium hypochlorite; under these conditions the enolate anion participates. Simple phenols whose reactivity is reduced by halogeno-substituents are rapidly oxidised in the form of enolate salts; this technique [7] was, however, ineffective for nitrophenol which is stable towards ruthenium tetraoxide.

We had difficulty in obtaining 5-methoxy-1-naphthol by hemialkylation of naphthalene-1,5-diol with methyl sulphate and 1 equiv. of alkali.[8] The Kuhn procedure [9] and another for hemialkylation of quinols [10] were also unsatisfactory, but adaption of Gates' method [11] for monobenzoylation of naphthalene-2,7-diol followed by methylation and removal of the benzoyl group gave an overall yield of 40% of 5-methoxy-1-naphthol. The selective dealkylation procedure with thioethoxide ion was published [12] after this part of our work was complete but it offers an attractive alternative route from the readily available dimethoxy-compound.

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Pyridine has been reported [13] to react violently with undiluted ruthenium tetraoxide but a controlled reaction was possible with the monoazanaphthalenes if a low equilibrium concentration of the tetraoxide in the two-phase system was used. A significant difference between quinoline and isoquinoline was that the pyridine ring was retained in the former reaction and disrupted in the latter. The quinoline reaction was slow and a good deal of material was recovered unchanged; however dimethyl pyridine-2,3-dicarboxylate was the only significant product and it was also formed in high yield by the rapid oxidation of quinolin-8-ol. The formation of phthalic acid as the only major fragment from the reaction of ruthenium tetraoxide with isoquinoline is a different result from those generally obtained by oxidation in solution [14] and in the vapour phase,[15] where pyridine-3,4-dicarboxylic acid is the major product. Oxidation by ruthenium tetraoxide is superior to ozonolysis for the degradation of aromatic compounds and gives products of a similar type. Thus phthalic acid, although often a minor product of isoquinoline oxidation, is formed as a major product on ozonolysis [16] and the pattern of fission of substituted naphthalenes [17] resembles that reported here and by Spitzer and Lee.[6]

EXPERIMENTAL

M.p.s were taken on a hot-stage apparatus. T.l.c was carried out on Merck silica gel HF_{254} with benzene–ethyl acetate (3 : 1) as eluant. I.r. spectra of Nujol mulls or of solutions in carbon disulphide were recorded with a Perkin-Elmer 237 spectrophotometer; the u.v. spectra of ethanolic solutions were taken with a Unicam SP 800 instrument. A Varian A-60A spectrometer was used for n.m.r. measurements in $CDCl_3$ and mass spectra were recorded by the Physico-Chemical Measurements Unit, Harwell.

Analytical g.l.c. was carried out with a Perkin-Elmer F11 chromatograph and for preparative work a Pye-Series-10s instrument was used with a 180 × 0·6 cm i.d. glass column packed with 5% Apiezon L on Chromosorb WHMDS (80—100 mesh).

Oxidation of Naphthols.—One example of each of the methods A—C is given; the yields obtained are summarised in the Table.

Method A: single phase of aqueous acetone with sodium periodate and hydrated ruthenium dioxide. 1-Naphthol (2·88 g, 20 mmol) in acetone (50 ml; reagent grade) at 20° was slowly added to a yellow solution of ruthenium tetraoxide, prepared from the dioxide (100 mg) (Engelhard Industries Inc.) by the action of sodium periodate (5 g) in aqueous acetone (75 ml; 1 : 2 v/v). The black precipitate of dioxide was discharged as soon as it appeared by steady addition of sodium periodate solution (10% in 1 : 1 water–acetone) until the colour of the tetraoxide persisted (*ca.* 30 g, 7 equiv. of periodate needed in total). The excess of oxidant was destroyed by addition of propan-2-ol (2 ml) and the solution was slowly filtered through Celite.* During concentration of the liquor, the vacuum distillation was interrupted, more acetone was added, and precipitated sodium iodate was filtered off before proceeding. The residue was extracted with hot ethanol (4 × 50 ml) and after addition of conc. sulphuric acid (0·5 ml) the combined extracts were refluxed for 3 h. The product (1·80 g) was isolated by concentrating the ethanolic solution, dilution with water, and extraction with ether. The esterified material was purified by preparative g.l.c. before characterisation. The product had u.v. ($\lambda_{max.}$ 278 and 285sh nm) and i.r. data ($\nu_{max.}$ 1715s, 1605m, 1585m, 1280s, and 742s cm^{-1}) and g.l.c. retention time (4·3 min) identical with those of diethyl phthalate.

Method B: two-phase system of aqueous sodium periodate and carbon tetrachloride. 1-Naphthyl acetate (1·86 g, 10 mmol) was dissolved in carbon tetrachloride (100 ml) and vigorously stirred with a solution of periodate (10%) containing ruthenium trichloride trihydrate (100 mg = 64 mg of $RuO_2,2H_2O$). Slow addition of the periodate solution was continued until a persistent yellow colour appeared in the organic phase; this was then separated and the tetraoxide destroyed with propan-2-ol, which was also added to the aqueous layer. It was possible to separate the dioxide from the organic solvent by filtration or centrifugation and t.l.c. showed that no starting material remained. No precipitate of the dioxide appeared in the aqueous layer, which was chilled before filtering off sodium iodate. Concentration and isolation of diethyl phthalate (1·10 g) as in Method A then followed.

Method C: two-phase system with sodium hypochlorite in place of periodate. 5-Methoxy-1-naphthol (0·87 g, 5 mmol; prepared as described below) dissolved in carbon tetrachloride (50 ml) was treated with ruthenium trichloride (50 mg) as for Method B but with sodium hypochlorite † (15% of available chlorine, *ca.* 20 ml in total) as the co-oxidant. After separation of the phases and destruction of the excess of tetraoxide the aqueous liquor was made just acid ‡ with strong sulphuric acid before concentration, esterification, and final purification by preparative g.l.c. at 170°. The principal product (0·62 g) was shown to be diethyl 3-methoxyphthalate [19] by its u.v. spectrum ($\lambda_{max.}$ 300 nm, slightly red-shifted from diethyl phthalate) and by i.r. absorption at $\nu_{max.}$ 2840 (OMe), 1785, and 1725 cm^{-1} (two differently situated CO_2Me). The molecular ion at *m/e* 252·0991 (Calc. for $C_{13}H_{16}O_5$: *M*, 252·0998) had daughter ions at 207 (*M* — OEt) and 179 (*M* — CO_2Et).

5-Methoxy-1-naphthol.—Naphthalene-1,5-diol (48 g) was treated with benzoyl chloride (100 ml) and a mixture of mono- and di-*O*-benzoyl derivatives was obtained as described by Gates.[11] The dibenzoate (38 g, 34%; m.p.

* Some finely divided ruthenium dioxide may penetrate this filter; if so all but the finest particles may be removed by passage through a VC type filter (0·1 μm; Millipore Filter Corporation).

† The oxygen demand of about 7 equiv. per mol of substrate requires large volumes of commercial bleach (3·5% of available chlorine). In these experiments it was more convenient to use stronger hypochlorite solution.

‡ Extraction of phthalic acids from aqueous liquors is difficult owing to their limited solubility in the common organic solvents. Of these the most satisfactory is ethyl methyl ketone, which should be dried azeotropically [18] before evaporation.

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240°; lit.,[8] 235°) was not extracted on treatment with ethanol; dilution of the extract afforded the monobenzoate (32 g, 41% after crystallisation from benzene), m.p. 160° (lit.,[20] 160°); $\nu_{max.}$ 3410 and 1720 cm^{-1}.

The monobenzoate (13·2 g, 0·05 mol) in acetone (100 ml) under nitrogen was treated with dimethyl sulphate (15 ml) in the presence of potassium carbonate (20 g) and sodium sulphite (1 g). After 3 h at 20° the mixture was diluted with water (250 ml) and the insoluble 1-benzoyloxy-5-methoxynaphthalene was separated in almost quantitative yield; recrystallisation from methanol gave material (11·6 g, 84%), m.p. 90° (lit.,[21] 102°). Hydrolysis of this product in methanol (40 ml) with potassium hydroxide (8 g) in water [20 ml; containing sodium sulphite (0·5 g)] under nitrogen yielded a clear solution; on treatment with carbon dioxide 5-methoxy-1-naphthol was precipitated and was crystallised from benzene (5·8 g, 80% yield); m.p. 140° (lit.,[22] 140°); $\nu_{max.}$ 3320 cm^{-1} (no carbonyl or benzenoid absorption). The overall yield in the sequence may be improved by omitting the recrystallisation steps used to characterise the intermediate monobenzoate and *O*-methyl benzoate.

Oxidation of Azanaphthalenes.—These experiments were conducted on a 20—40 mmol scale and only for quinoline was any unchanged material detected after the given (Table) reaction time. The residues from evaporation of the neutral liquors were worked up as for Method C with final purification by preparative g.l.c. The dimethyl pyridine-2,3-dicarboxylate was characterised by its m.p. (55°; lit.,[23] 54°), its mass spectrum [M^+ 195 ($C_9H_9NO_4$)], and its n.m.r. spectrum [δ 7·65 (5-H), 7·06 (3-H), and 6·33 (4-H); $J_{3,4}$ 8·0, $J_{4,5}$ 6·0, $J_{3,5}$ 2·0 Hz].

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