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The Oxidation of Homophthalimide Derivatives by Dioxygen in Alkaline Media and Cleavage-Cyclisation Reactions

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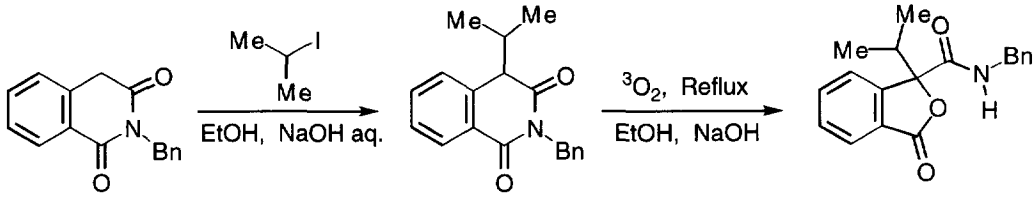
Abstract: The oxidation of α-alkylhomophthalimide derivatives by dioxygen in the presence of ethanolic sodium hydroxide leads to the rapid formation of α-hydroxy-α-alkylhomophthalimide derivatives and hence, as a result of ring cleavage and lactone formation, to α-amido-α-alkylphthalides, potential precursors to phthalide isoquinoline alkaloids and analogues. © 1997 Elsevier Science Ltd.

The chemistry of dioxygen is of considerable current interest in view of its impact on our understanding of a range of chemical and biological reactions.[1] The cleavage of ketones by oxygen as a result of the formation of α-hydroperoxyketones has been reported many times, particularly when the ketone forms a stable enol.[2] Even simple ketones are have been shown to react with oxygen in a strongly basic medium.[3] The autoxidation of ketones can take place without the cleavage of the carbon chain as exemplified by the α-hydroxylation of (–)-isorotenone,[4] a number of steroidal 20-ketones,[5] and sesquiterpenoids[6] and triterpenoids,[7] as well as the γ-hydroxylation of α,β-unsaturated ketones such as cyperone.[8] The direct oxygenation of enolates, generated by anionic oxy-Cope rearrangement reactions, has been reported more recently in connection with the synthesis of polycyclic α-hydroxy ketones,[9] and hydroxylation α- to an aryl ketone has also been reported as part of the pinene pathway to taxanes.[10] Other carbonyl compounds such as esters[11] and dialkylmaleic anhydrides[12] have also been shown to give autoxidation products that involve reactions of carbanions. The ease of formation of 3-hydroxy-1,3-dimethyl-5-methoxyoxindole during the asymmetric alkylation of 1,3-dimethyl-5-methoxy-oxindole may well be related to the aromatic character of the enolate of the amide function.[13] The autoxidation of esters and amides to the related α-hydroxy-derivatives has been studied using titanium enolates[14] and a recent report is concerned with the oxidation of anions derived from a series of β-imidoesters using dibenzoyl peroxide.[15] It has been pointed out that the ease of oxidation of ionizable organic compounds depends not only on the degree of conversion to an anion but also on the relative stabilities of the carbanions and the related radicals.[16] For example, in a β-di-carbonyl system the enolate ion is more stabilized than the related radical and hence the latter is more difficult to form. It is therefore entirely in accord with expectation that the β-imidoesters could not be oxidised cleanly by dioxygen.[15] As far as we are aware reactions of imides with dioxygen in the presence of a base is without precedent.[17] The report on the reactions of ethyl 2-aryl-1,3(2*H*,4*H*)-dioxoiso-quinoline-4-carboxylates[15] prompts this letter in which we record our observations concerning the autoxidation of some 4-alkylisoquinoline-1,3(2*H*,4*H*)-diones.

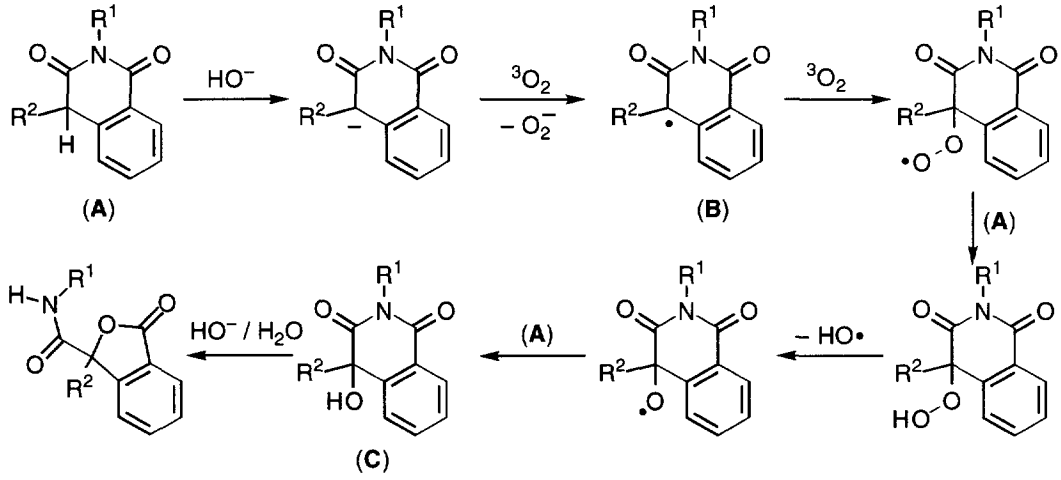
The formation of enolate ions from *N*-substituted derivatives of homophthalimide is particularly easy and has been used by us previously in order to introduce two alkyl residues at the benzylic carbon.[18] In the case of the reaction of *N*-benzylhomophthalimide with methyl iodide in aqueous ethanolic sodium hydroxide the reaction proceeds rapidly with the formation of the dimethyl derivative. The greater steric requirement of the isopropyl group suggested that the formation of the monoalkylated derivative (**1**) would be straightforward and this has been confirmed by experiment. When a solution of (**1**) in ethanolic sodium hydroxide was saturated with

dioxygen and then heated under reflux the fluorescence was discharged after about three hours and gave a quantitative yield of a product that had incorporated an additional oxygen atom and where the two carbonyl stretching frequencies in the infrared spectrum of the original homophthalimide (ν_{max} 1670 and 1714 cm^{-1}) had been replaced by two new absorptions (ν_{max} 1676 and 1773 cm^{-1}). An accurate mass measurement on the mass spectrometric molecular ion established the molecular formula and the ^1H and ^{13}C nuclear magnetic resonance spectra[19] confirmed the structure of the lactone (**2**) in which a ring contraction from the six-membered to a five-membered ring had occurred. It is important to note that the reactions do not proceed in the absence of base. Ring contraction reactions from a six-membered to a five-membered ring have been reported previously, and are exemplified, for example by the conversion of *N*-substituted isoquinolinetriones into ethyl 3-hydroxyiso-indolone-3-carboxylates by heating in ethanol in the presence of triethylamine.[20]



(**1**) (**2**)

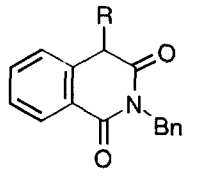
The reaction conditions used suggested the intermediacy of a tertiary hydroperoxide but, as with the α-ketohydroperoxide derived from cyclohexanone which is apparently very unstable,[21] we were unable to detect a hydroperoxide by the starch-iodide test. The latter result suggested that the reaction could be catalytic in base and a reaction in the presence of 15 mol% of sodium hydroxide also gave the lactone (2) in high yield. A mechanistic sequence that accounts for the observed results is shown in the **Scheme**. It is clear that a number of alternative routes are available to the initial radical (**B**), for example the involvement of the hydroxyl radical in that step would also regenerate hydroxide ion. By carrying out the oxidation reaction using a catalytic amount of sodium hydroxide in the presence of an excess of triethyl phosphite[22] and a continuous supply of dioxygen, we were able to stop the isomerisation of the proposed hydroxyhomophthalimide (**C**, R^1 = Bn, R^2 = ^{i}Pr). In the latter reaction the compound (**3**) was isolated in 97% yield together with a small amount of recovered starting material (**1**).



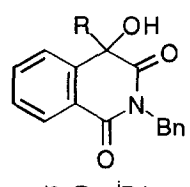
Scheme

We have also prepared the ethyl analogue (**4**) of the compound (**1**) and find that it is converted more slowly than the compound (**1**) and gave, after 9h a similar lactone (**6**) in 25% yield together with a second product that was formed in 36% yield in a reaction using a catalytic quantity of sodium hydroxide. The products were separated by flash chromatography and the second product was shown to be the expected intermediate hydroxyhomophthalimide (**5**). The hydroxyhomophthalimide (**5**) was converted into the phthalide derivative (**6**) in a quantitative yield when it was heated under reflux in ethanolic sodium hydroxide solution. The benzyl derivative (**7**) was shown to react even more slowly than the ethyl derivative (**4**) and gave the hydroxy compound (**8**) in 33% yield together with the lactone (**9**) in 11% yield and unchanged starting material (56%) when the reaction was allowed to proceed for 17h using a catalytic quantity of sodium hydroxide. A substituent is clearly required on the benzylic carbon in a homophthalimide for the autoxidation to proceed; we found that N-benzylhomophthalimide does not undergo the autoxidation reaction under the conditions reported herein.

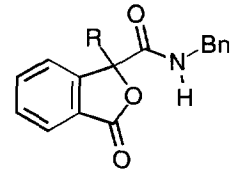
The preparation of lactonic amide precursors for Bischler-Napieralski cyclisation reactions that can lead to phthalide-isoquinoline alkaloids[23] is frequently troublesome.[24] It is clear that our new procedure provides a straightforward route to amidophthalides which, if the group R^1 in (**A**) was a β-arylethyl residue, could function as key intermediates in Bischler-Napieralski cyclisation reactions *en route* to phthalideisoquinoline alkaloid analogues which are potent central nervous system active compounds.[25] A number of other phthalides have also been shown to have interesting biological properties.[26] The majority of the compounds isolated have not formed good crystals and we were therefore pleased that the tryptamine analogue (**10**), m.p. 187-189 °C, was obtained in a suitable form for an X-ray crystallographic study.[27] The stereochemical features shown in the figure explain the large chemical shift differences exhibited in the ^1H nmr spectrum for the diastereotopic methyl groups.



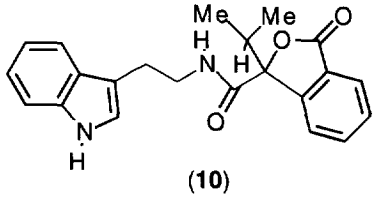
(**4**, R = Et)
(**7**, R = Bn)



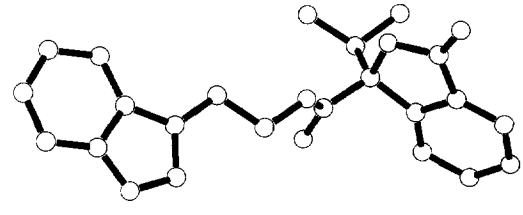
(**3**, R = ^{i}Pr)
(**5**, R = Et)
(**8**, R = Bn)



(**6**, R = Et)
(**9**, R = Bn)



(**10**)



figure

In conclusion, we have developed a mild protocol that allows the direct oxygenation of tertiary benzylic imide centres that not only produces compounds of potential biological interest, but also produces phthalides by ring cleavage and recyclisation that are potential precursors to phthalideisoquinoline alkaloids.

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19. $M^{+\cdot}$ found: 309.1363, $C_{19}H_{19}NO_3$ $M^{+\cdot}$ requires: 309.1365: δ_H 400 M Hz ($CDCl_3$) 0.56 (d, 3H, J = 6.8 Hz), 1.14 (d, 3H, *J* = 6.8 Hz), 2.86 (h, 1H, *J* = 6.8 Hz), 4.22 - 4.63 (o, 2H, AB of ABX), 7.06 (br, 1H, X of ABX N*H*), 7.22 - 7.88 (m, 9H) ppm; δ_C 100.6 M Hz ($CDCl_3$) 15.35 (Me), 17.76 (Me), 35.52 (CH), 43.77 (CH_2), 92.06 (C), 123.71 (CH), 124.61(C), 125.65 (CH), 128.02 (CH), 128.22 (CH), 128.96 (CH), 130.02 (CH), 135.16 (CH), 137.60 (C), 149.06 (C), 169.30 (C=O), 169.76 (C=O) ppm.
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27. Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited with the Cambridge Crystallographic Data Centre.

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