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PHOTOCHEMICAL HYDROGEN ABSTRACTION AND CYCLISATION IN MALEIMIDE DERIVATIVES

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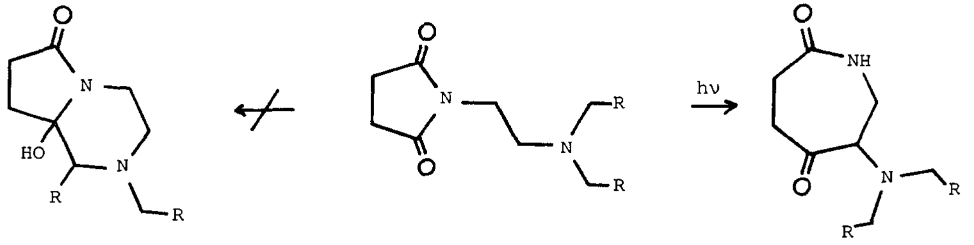
Summary: N-(2-Morpholinylethyl) derivatives of maleimide, 3,4,5,6-tetrahydrophthalimide and phthalimide give rise to products with a new hexahydropyrazine ring, in contrast to the corresponding derivative of 1,2,3,6-tetrahydrophthalimide which gives an octahydrobenzazepinedione.

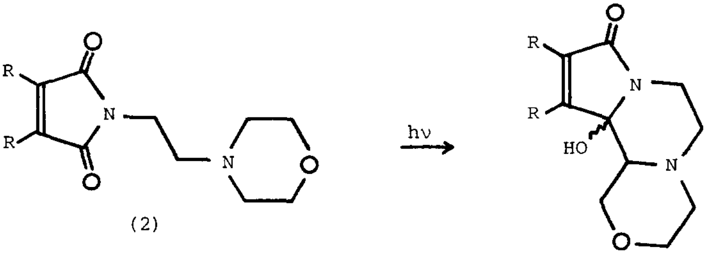
The photochemistry of imides has received considerable attention recently,[1] and one feature of the results is a consistent difference between aromatic (e.g. phthalimide) and aliphatic (e.g. succinimide) derivatives. For example, succinimides give oxetanes on irradiation with alkenes,[2] but phthalimides give benzazepinediones by incorporation of the alkene into the imide ring,[3] and only in a few phthalimide systems have oxetanes been found.[4] The hydrogen abstraction and cyclisation reactions of N-substituted phthalimides provide a good route to multicyclic products with new heterocyclic rings ranging in size from 5 to 38 atoms, but the reaction is much more restricted for succinimide derivatives. Compounds with new 5-membered rings can be made readily from N-substituted succinimides,[5,6] and new 7- and 8-membered rings can be formed in poor yield;[6] however, N-(dialkylamino)ethylsuccinimides give azepinediones (1),[5,7] rather than pyrrolo[1,2-a]pyrazine derivatives analogous to those obtained from the corresponding phthalimides.[8]



(1)

The differences between aromatic and aliphatic systems can be attributed to the greater electron-acceptor ability of the imide ring in the excited states of the former, and the greater involvement of electron transfer and radical ion species in the photochemistry of phthalimides. If this is correct, then the use of unsaturated alicyclic imides (i.e. maleimide derivatives) might provide a route to pyrrolopyrazine products without the benzo-fused ring of the phthalimide photoproducts.

N-Substituted maleimide derivatives (2) were prepared, and irradiated (medium pressure mercury arc, quartz filter, acetonitrile solvent). In each case the major isolated products were diastereoisomeric compounds with a new hexahydropyrazine ring.[9] Structural assignment was based on the results of elemental analysis and spectroscopic evidence: for example, the infrared spectrum of the major maleimide product showed bands for hydroxyl (3350 cm^{-1}) and 5-membered lactam C=O (1700 cm^{-1}) groups; the ^{1}H-n.m.r. spectrum indicated that two non-equivalent alkene protons were present (doublets at 6.9 and 6.2 ppm) and that the morpholine ring was no longer intact; the ^{13}C-n.m.r. spectrum showed signals for a single amide carbonyl (170 ppm), two non-equivalent alkene carbons (145 and 129 ppm), a quaternary N-C-OH carbon (86 ppm), and four non-equivalent carbons in the morpholine ring (67, 67, 66 and 54 ppm). Interestingly, the morpholine signals in the ^{13}C-spectrum for the minor diastereoisomer are shifted considerably (67, 63, 61 and 44 ppm); this is an effect that we have found for several other pairs of diastereoisomers in similar systems (including phthalimide photoproducts), and it can be attributed in part to the more cage-like structure of the isomer in which the bridgehead H and OH groups are *cis*; this holds some of the atoms fairly close to the main shielding regions of the unsaturated group.

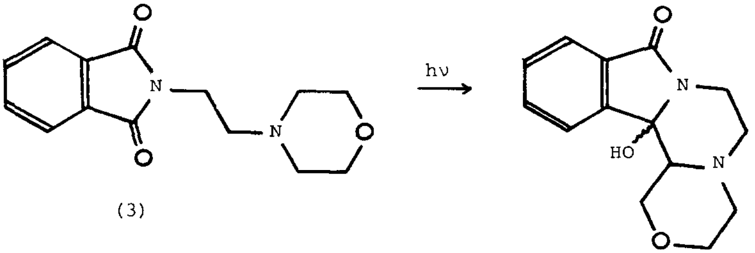


(2)

33% (R=H)

37% (R,R=$(CH_2)_4$)

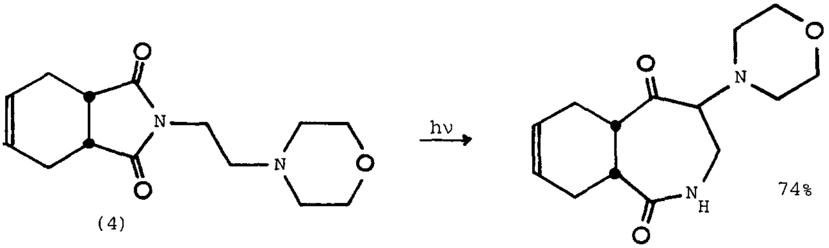
The photoreactions of maleimides are normally dominated by reaction at the C=C double bond, and this is the first example of a photochemical cyclisation involving a substituent on the nitrogen. For comparison, we irradiated (Pyrex) the corresponding phthalimide (3), which has not previously been reported, and isolated the two diastereoisomers of the product with a new hexahydropyrazine ring.



(3)

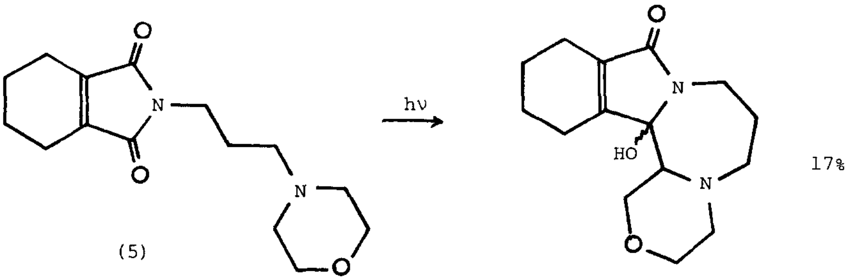
43%

N-(Dialkylaminoethyl)phthalimides such as (3) give pyrrolopyrazines on irradiation, and so they cannot be used to afford entry into the benzazepinedione series - compare reaction (1) for succinimides. To circumvent this difficulty, the 1,2,3,6-tetrahydrophthalimide (4) was prepared, and irradiated to give a high yield of a single compound. The presence of ketone and amide carbonyls, the absence of hydroxyl, and the presence of a symmetrical morpholine ring, all point to the octahydrobenzazepinedione structure, which is consistent with all the other data obtained for the compound. The success of this reaction is particularly pleasing in the light of a report[7] that N-ethyl-1,2,3,6-tetrahydrophthalimide gives only a cyclobutane dimer on irradiation.



(4)

We also prepared and irradiated an analogue (5) of the maleimides with an extra methylene group between the nitrogen atoms. The products isolated were diastereoisomers of a compound with a new perhydro-1,4-diazepine ring, although the yield was low. Analogous products have been reported[8] from N-(dialkylaminopropyl)phthalimides, often in reasonable yield, and because the morpholine derivative (6) had not been included in these reports, we prepared and irradiated (Pyrex) this substrate. Rather surprisingly, five products were obtained (three of them could not be isolated completely pure, but only as a mixture with one of the other products), of which the major was a photoreduced compound,[10] despite the use of acetonitrile (a poor hydrogen donor) as solvent. The formation of both pyrrolizidine and pyrrolodiazepine products suggests that there are some limitations on the generally recognised photocyclisation reaction of phthalimides.



(5)

The isolation of photocyclised products from N-substituted maleimides is consistent with the idea that an electron-transfer mechanism contributes to the formation of medium- and large-ring systems in the photochemistry of phthalimides, and it is possible that a range of macrocyclic compounds can be prepared also from maleimide derivatives.

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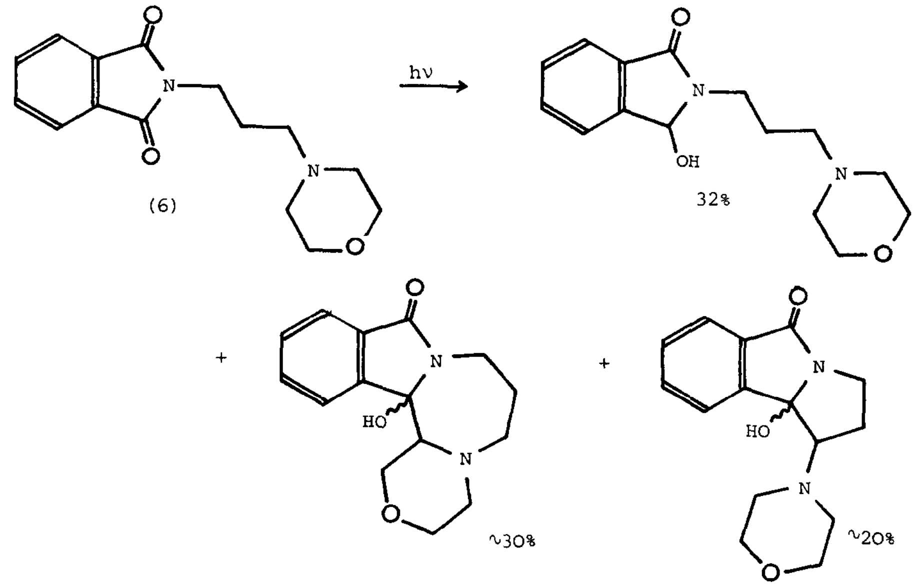

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