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Photochemical Dimerization Reactions of N-Acylindoles[1]

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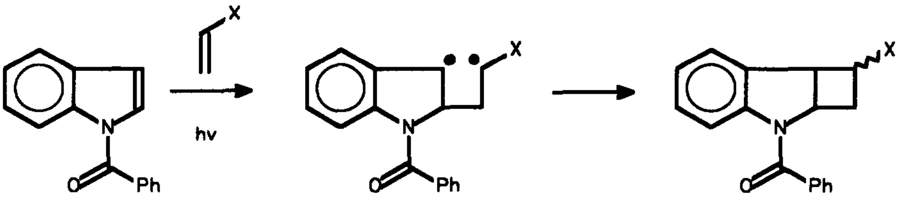
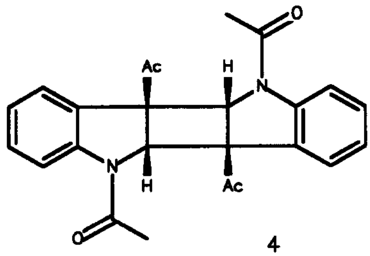
Key Words: N-acylindoles; photochemical dimerization of indoles; cyclobutane adducts; head-to-head regioisomers.

***Abstract:** The photochemical dimerization of N-acylindoles is reported. Cyclobutane adducts are formed and result from bonding between the 2-positions and 3-positions of the indole rings. Chemical yields of cycloadducts are enhanced by the use of acetophenone as a triplet sensitizer. The anti head-to-head regioisomers of the photodimers are formed predominantly. Contrary to previous reports, N-acetylindole was also observed to yield photodimerization products.*

Ultraviolet light irradiation of N-aroylindoles and N-acetylindole in the presence of alkenes leads to regioselective cyclobutane formation by addition of the alkene termini to the 2- and 3-positions of the 5-membered ring of the heterocycle.[2,3] The analogous reaction does not proceed for indole itself.[2-4] We have examined the mechanism of this reaction[5-13] and have found that the lowest singlet excited state of N-aroylindoles is a charge-transfer state[5,6] and is not involved in cycloaddition. Direct irradiation of N-benzoylindole or N-ethoxycarbonylindole results in photo-Fries rearrangement,[7] and production of 3-benzoylindole or 3-ethoxycarbonylindole, respectively, as the major products. If alkenes are present, then they react with the triplet excited state[8] of the indole derivative to form triplet 1,4-biradicals[9] which either ring close to cycloadducts or revert to ground state starting materials.[8,9] For N-benzoylindole the biradicals are apparently formed by bonding of the 2-position of the indole to the less substituted end of the alkene (Scheme 1).[10,11] The photocycloaddition reaction of N-acyl indoles with alkenes, and methods for the subsequent removal of the N-activating group from the adducts, has been examined for a wide variety of N-acylindoles.[12]

SCHEME 1





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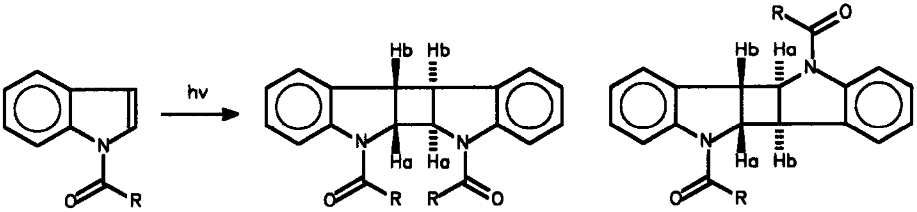
During an investigation of the potential intramolecular photochemical cycloaddition reaction of N-vinyloxycarbonylindole, **1a**, a compound identified by mass spectroscopy as a photodimerization product was isolated in the absence of the desired intramolecular photoadducts. Although many examples exist of the photodimerization of indene, benzofurans, and benzothiophene 1,1-dioxides,[14-18] we are aware of only one published example of an indole photodimerization reaction. This involved ultraviolet light irradiation of 1,3-diacetylindole to yield a single product which was shown by x-ray crystallography to be the head-to-tail dimer **4**.[19,20] The authors reported that other indole derivatives such as N-acetylindole did not yield photodimers under their conditions. The photodimerization of **1a** therefore represents a new example of a very rare reaction pathway for the indole system. In order to investigate the generality of this reaction, additional irradiations were carried out using N-ethoxycarbonylindole, **1b**, N-benzyloxycarbonyl-indole, **1c**, N-phenoxycarbonylindole, **1d**, and N-acetylindole, **1e**, and the stereochemistry and regiochemistry of the dimers formed were determined.

Ultraviolet light irradiation[21] of **1a-d** resulted in the formation of photodimerization products **2a-d** and **3b-d** with the yields[22] shown in Scheme 2. Initial structural assignment of each dimer was based on the observation of a molecular ion in the mass spectrum which was twice the molecular weight of the respective N-acylindole.[23] The ^{13}C-n.m.r. spectra obtained appeared similar to those of the parent N-acyl-indoles except that the two aromatic methine signals of the pyrrole ring had been replaced by two sp^3 methine carbon signals; this is consistent with 2+2 dimerization by bonding between the 2- and 3-positions of the indole moieties. In addition, only half the expected number of carbon signals were observed indicating that the dimers were symmetrical in structure.

SCHEME 2



1a	R = $OCH{=}CH_2$	**2a**	(5%)		
1b	R = OCH_2CH_3	**2b**	(59%)	**3b**	(29%)
1c	R = OCH_2Ph	**2c**	(19%)	**3c**	(7%)
1d	R = OPh	**2d**	(56%)	**3d**	(12%)
1e	R = CH_3	**2e**	(18%)	**3e**	(3%)

The ^{1}H-n.m.r. spectra of the isolated products suggested the regiochemistry of photodimers **2a-d** to be head-to-head. Signals at *ca.* 6.6 p.p.m., corresponding to the 3-position proton of an indole ring, were absent while each dimer exhibited two signals at *ca.* 4-5 p.p.m.; these were assigned to protons H_a and H_b. For each dimer the signals assigned to H_a and H_b were both doublets ($J \approx 7$ Hz) and were coupled to each other. If the photodimers possessed the head-to-tail structure then H_a and H_b would be expected to appear as triplets or doublets of doublets. The *cis* relationship of H_a and H_b was assigned on the basis of the magnitude of the coupling constants and the prohibitive strain which would be present in a *trans*-fused system. The regiochemical assignment was confirmed for **2d** by x-ray structure determination;[24] this also revealed that the stereochemical arrangement of the indoline rings is *anti*. The structures of the dimers **2b** and **2c** were confirmed by their formation from **2d** on treatment of the latter with the sodium salt of the appropriate alcohol. With the N-acylindole **1a** only a single dimer was isolated. The structure of this dimer was confirmed as **2a** by conversion to **2b** by hydrogenation.[25]

The ^{1}H-nmr spectra of the minor dimerization products **3b-d** were similar to those of **2b-d** in that H_a and H_b were both doublets. However, the x-ray structure obtained[24] for **3b** indicated it to be the *anti* head-to-tail dimer; consequently the *anti* coupling constant between H_a and H_b must be zero. The structures of **3c** and **3d** were determined by conversion to **3b** by treatment with ethoxide.

Two dimers were obtained from irradiation of N-acetylindole **1e**; by analogy with the products obtained from the N-acylindoles **1a-d**, these are tentatively assigned structures **2e** and **3e**.

As expected for the bimolecular process shown in Scheme 2, increasing the concentration of N-acylindoles **1a-d** reduced irradiation times and increased chemical yields. Inclusion of acetophenone as a triplet sensitizer had a similar effect, suggesting that the quantum yield of intersystem crossing of the N-acylindoles, Φ_{isc}, is less than unity.[26] The inclusion of acetophenone not only accelerated the reaction but also served to inhibit the formation of photo-Fries products.[7] This competing process consumes the starting material and also impedes the formation of the desired photodimers since the photo-Fries products absorb light efficiently. We have previously shown[7] that whereas the cycloaddition reaction proceeds from the lowest triplet excited state of the N-acylindole, the photo-Fries reaction likely proceeds from an upper singlet excited state or a vibrationally hot form of the lowest singlet excited state. Thus the photo-Fries reaction can be suppressed in favour of the photodimerization reaction by use of a sensitizer with a triplet energy higher than that of the N-acylindoles (69 kcal/mol from phosphorescence measurements at 77 K).

The results described here suggest that the photochemical dimerization of N-acylindoles is a general reaction pathway, contrary to previous reports.[20] In addition, unlike 1,3-diacetylindole, which was found to yield the *syn* head-to-tail dimer,[20] the N-acylindoles examined yield the *anti* head-to-head regioisomer predominantly. Our results reveal that the photodimerization reaction of N-acylindoles must be taken into account if alternative photochemical products are desired, such as 1:1 cyclobutane adducts from reaction with alkenes, or photo-Fries rearrangement products. The photodimerization reaction may also provide a route to the as yet unreported dimer of indole if the acyl substituent can be removed from the N-acylindole dimers. This interesting possibility is currently under investigation in our laboratory.

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19. In this nomenclature, derived from that commonly used in enone cycloaddition photochemistry, the "head" of the indole molecule is the nitrogen atom.
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21. Irradiations were performed in benzene using Pyrex and water filtered light from a medium pressure mercury lamp. Acylindole concentrations were 2M; acetophenone sensitizer concentrations were 1.5M.
22. The dimers were separated by chromatography and fractional crystallisation.
23. Molecular ion determinations were carried out using chemical ionization mass spectrometry; electron impact ionization resulted in rapid cleavage of the cyclobutane ring to regenerate the monomer.
24. Dimer **2d**; $a=14.055(3)$, $b=16.072(3)$, $c=12.384(3)$ Å, $\beta=91.30(2)°$, $T=23°C$, space group $P2_1/c$, $Z=4$, $R=0.079$, $Rw=0.047$. Dimer **3b**; $a=11.165(2)$, $b=6.502(1)$, $c=12.737(1)$ Å, $\beta=98.55(1)°$, $T=-30°C$, space group $P2_1/c$, $Z=2$, $R=0.061$, $Rw=0.052$. Full details of the x-ray structure determinations will be reported in a full paper.
25. Treatment of **2a** with palladium on barium carbonate under an atmosphere of hydrogen resulted in hydrogenation of the double bond of the N-acyl substituent and formation of **2b**.
26. Recent results estimate Φ_{isc} to be *ca.* 0.32 for N-ethoxycarbonylindole. See ref. 12.

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