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REGIOSELECTIVITY OF THE PHOTO-FRIES REARRANGEMENT IN ACETOXYINDOLES

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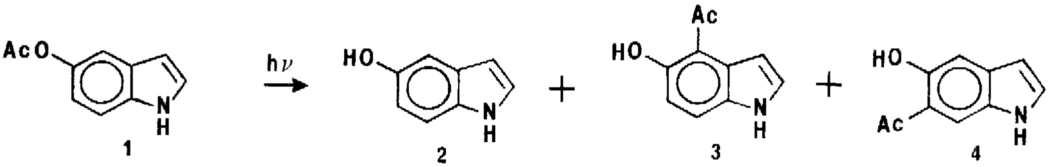
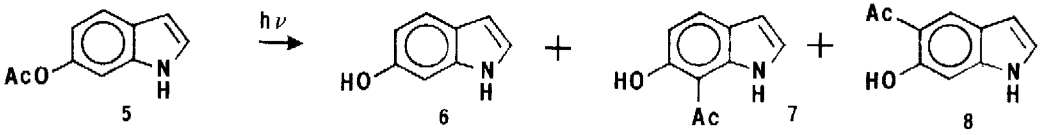
Abstract 5- and 6-acetoxyindoles have been found to undergo regio-selective photo-Fries rearrangement in aqueous solution.

The photochemistry of indoles has been extensively studied.[1,2] Indoles substituted at the 5 and 6 positions are of particular interest[3] since they are building blocks of melanin pigments.[4] To better understand the photochemistry of melanins, a study of the photochemistry of substituted indoles in aqueous buffered media at physiological pH was undertaken.

Both acetoxyindoles **1** and **2** were found to undergo the photo-Fries rearrangement[5,6] to yield three primary products.





Interestingly, the acetyl group in **1** migrates preferentially to the 4-position of the indole ring, and the same group in **5** migrates preferentially to the 7-position (Table 1). It appears that the rearrangement in these acetoxyindoles is regioselective.

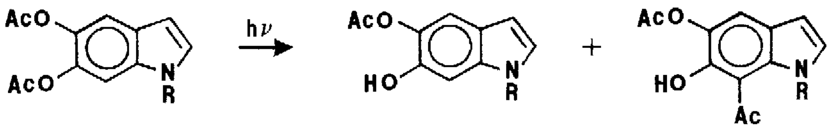
The photochemistry of 5,6-diacetoxyindoles has also been studied. **9a** gives two major products, **10a** and **11a**.[7,8] Similarly, **9b** gives **11b** as the major rearrangement product [9] (Table 1). The results indicate that the cleavage of an acetoxy group in this indole system is also selective. Only a small amount of the corresponding products can be detected when acetone is used as the triplet sensitizer. Thus, the rearrangement most likely occurs from the singlet excited state.

Table 1: CHEMICAL YIELDS OF PHOTOPRODUCTS[a]

Indole	Fragmentation		Rearrangement[b]			
1	2	(>36)	**3**	(40)	**4**	(6)
5	**6**	(10)	**7**	(66)	**8**	(7)
9a	**10a**	(30)	**11a**	(66)		
9b			**11b**	(>83)		

[a] Percentage yield of each product is given in parentheses.

[b] Reference 7.



9 **10** **11**

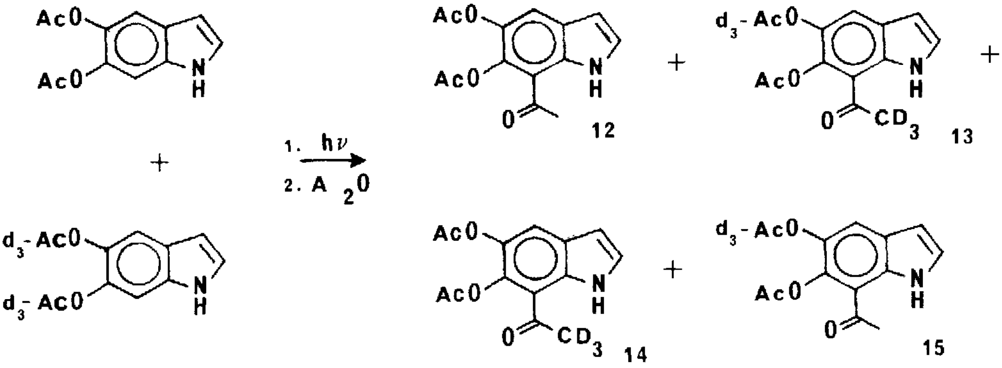
9-11a, R = H

b, R = CH_3

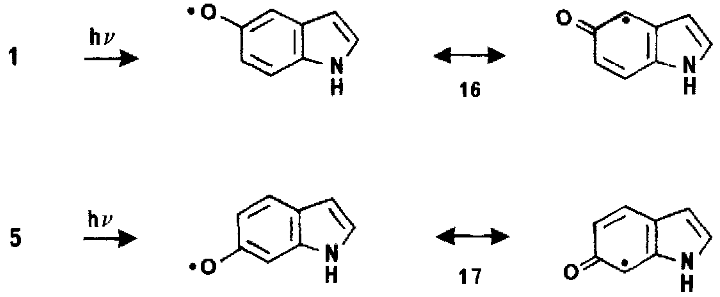
To understand the greater reactivity of the 6-acetoxy group, the relative quantum yields of consumption of **1**, **5**, and **9a** were measured. Both **5** and **9a** have similar efficiency, but **1** is only half as reactive. This indicates that the electronically excited 5-acetoxy chromophore may have a more efficient deactivation pathway than the 6-acetoxy. Alternatively, the excitation energy may locate preferrentially on the 6-acetoxy substituent. Hence mainly 6-acetoxy cleavage can be seen. It is not clear which of these two possibilities is more likely, but the product distribution from the photolysis of **9** seems to favor the latter.

Both concerted and free radical mechanisms[10] have been proposed for the photo-Fries rearrangement reactions. To determine the reaction pathway of the present acetoxyindoles, equimolar amounts of acetoxy-deuterated-d_6 and non-deuterated **9a** were photolysed.[6] If the rearrangement takes place via a concerted pathway, only products **12** and **13** should be obtained after the acetylation of the primary products (Scheme). On the other hand, two additional products, **14** and **15**, should also form when the free radical mechanism plays an important role. Mass spectrometric analyses of the mixture show significant label scrambling.[11] Hence, the rearrangement must arise from the combination of a free acyl radical and a free indoloxy radical.

Scheme



The regioselective rearrangement is probably due to greater electron density at the 4 or 7 position of indoloxy radical **16** or **17**.[12] Recombination of the acyl radical with **16** or **17** gives either starting material or rearrangement products.



In conclusion, this study demonstrates that the pyrrole ring has a large directing (not steric) effect on the photo-Fries rearrangement in the acetoxy-indole system. This effect is not observed in the photolysis of hydroxyphenylacetates or heterocyclic esters[13]. Not only is the migration of the acetyl group regioselective in the 5- or 6-substituted acetoxyindoles, the cleavage of the acetoxy groups is also highly selective (i.e., the 6-acetoxy group cleaves predominantly in **9**).

Acknowledgment

We would like to thank Drs. Y.-G. Pan and T. Schultz at Clairol for their helpful discussions in systheses and Dr. D. Batcho of Hoffmann-La Roche for the generous gift of 6-benzyloxyindole, which is an intermediate to compounds **5** and **6**.

References and Notes

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[6] All solutions were photolyzed under positive N_2 pressure in an immersion well apparatus equipped with a 450W medium pressure mercury lamp and a Pyrex sleeve. The reactions were stopped after 40-50% conversion of the starting material. Products were identified by comparing the retention times on HPLC chromatogram with authentic samples, or their structures were determined by ^{1}H NMR, infrared, and mass spectroscopies after derivatization by acetylation. Since the acetylation of hydroxyindoles is quantitative, the yields of acetoxy derivatives actually represent the yields of **3**, **4**, **7**, **8**, and **11**, respectively.

[7] **7** and **11** were acetylated after the photolysis, and the structures were confirmed by spectroscopic methods. The N-H proton in acetylated **7** and **11a** shifts 1-2 ppm more downfield than the corresponding **3**, **4**, and **8** derivatives in ^{1}H NMR spectra. Furthermore, both C=O stretching frequencies in the infrared spectra of **7** and **11a** are lower than that when the acetyl group is at 4, 5, or 6 position. This is probably due to the hydrogen bonding between the N-H and the carbonyl at the 7-position. Schwartz, A.; Pal, Z.; Szabo, L. **J. Heterocyclic Chem. 1987, 24**, 651-4.

[8] Products **10** and **11** were also trapped by benzylation with benzylbromide in acetone solvent. Both final products gave satisfactory MS and ^{1}H NMR analyses.

[9] **11b** was acetylated and identified as mentioned in ref. 8. The chemical yield of **11b** in Table 1 was determined by ^{1}H NMR.

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[11] All three molecular ion peaks, viz., m/e=275(**12**), 278(**14+15**), 281(**13**) were present in the mass spectrum of the photoproduct. A mixture of deuterated and non-deuterated **9a** shows no scrambling of labels in the mass spectrometer probe. m/e=278 must be due to the presence of compounds **14** and **15**.

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