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PHOTOCHEMICAL REARRANGEMENTS FOR THE SYNTHESES OF 3-, 4-, AND 6-SUBSTITUTED INDOLES

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Indole derivatives having substituents at the 4- and 6-positions are of interest because of their significant biological activities. However, their synthesis by hitherto used methods is time-consuming and requires a series of reaction steps from a starting material having the necessary substituents in the benzene moiety.

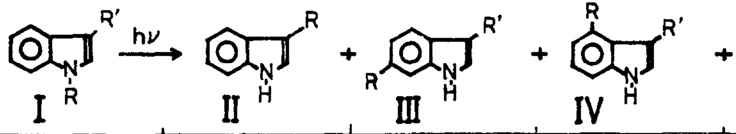
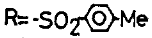
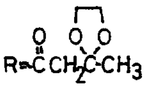
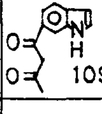
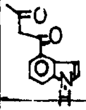
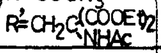
We wish to describe here[1] the direct introduction of various kinds of side chain units into the 3-, 4-, and 6-positions of the indole ring by Fries type photochemical rearrangement of readily available 1-substituted indoles.

I) Rearrangement of Carbon Units[2]

i) Non-Substituted Indoles

Irradiation of an ethanol solution of 1-ethoxycarbonylindole (Ia) with a Hanovia 450-W high-pressure mercury lamp in nitrogen atmosphere[3] afforded 3-, 4-, and 6-ethoxycarbonylindole (IIa, IIIa, IVa) and diindolylmethane in 46.5%, 23.1%, 8.8%, and 1.4% yields, respectively, in addition to a low yield of indole and many minor unknown products. The structural proof of IIa, IIIa, and IVa was easily obtained by inspection of the nmr spectra of the corresponding N-acetyl derivatives. In these compounds, the C-7 proton was clearly discernible from other protons because of the deshielding effect of the acetyl group. Thus, it appeared as a multiplet in the 3-substituted indole, but as a doublet and singlet in the 4- and 6-substituted indoles, respectively. The structures of the products shown in Table I were determined similarly. When the compound If was irradiated in benzene, IIf, IIIf, and IVf were obtained, though deketalization of the products occurred to a significant extent to afford additional products, 4- and 6- acetoacetylindole,

Table I. Photochemical Rearrangements of Various 1-Substituted Indoles.

Starting materials	Products	Yield (%) mp (°C)		
				Other products
a) R = COOEt R' = H	46 5 % 124 5 - 125 5°	23 1 % 72 - 73°	8 8 % 69 - 71°	diindolyl methane 1 4 % 163-165°
b) R = $COCH_3$ R' = H	6 5 190 - 191°	20 122 - 122 5°	8 0 163 - 164°	2-acetyl deriv 1.2 % 153-154°
c) $R=\overset{O}{\overset{\|}{C}}(CH_2)_2\overset{O}{\overset{\|}{C}}OMe$ R' = H	35 6 116 - 117°	24 0 107 5 - 108 5°	7 7 101 5 - 102°	indole
d) R = $CH_2\phi$ R' = H	36 1 108 - 109°	5.8 *	6 7 79 0 - 80 0°	—
e)  R' = H	23 7 176 - 176 5°	17 6 176 - 176 5°	1 6 189 - 190°	indole
 f) R' = H	29 4	18 0	7 5	unknown product 3.7 % 134-135°
	—	 15 8 109 - 110°	 8 6 119 - 120°	
irradiated in benzene	35 0 155.5 - 156 5°	13 7 138 5 - 139 5°	4 4 115 - 116°	〃 2 % 134-135°
g) R = $COCH_3$ R' = Me	—	20 0 167 - 168°	2 0 153 - 153 5°	2acetyl skatole 15 % 143-144°
h) R = $COCH_3$  $R'=CH_2C\begin{smallmatrix}(COOEt)_2\\NHAc\end{smallmatrix}$	—	30 0 214 - 215°	—	2-acetyl deriv 12 % 145-146°
i) R = $COCH_3$ R' = COOEt	—	24 4 167 - 168°	—	unknown oil 9 9 %
j) R = $-CH_2CH=C\begin{smallmatrix}Me\\Me\end{smallmatrix}$ R' = H	34 0 49 - 50 0°			
k) R = $-COCH_2COCH_3$ R' = H	12 1 144 - 145°			
l) R = $-COCH=C\begin{smallmatrix}Me\\Me\end{smallmatrix}$ R' = H	21 5 136 5 - 138°			

* The 6-benzyl compound was detected as 1,3-diacetyl-6-benzylindole (mp 135.5-136.5°). 95.0% Ethanol was used as a solvent in all the experiments shown in this table.

when ethanol was used as a solvent. From the results of the rearrangement of the 1-substituted indoles (Ia-If) we have established the general order of positional reactivity of the indole molecule as 3>6>4>2. Changes in concentration, temperature, light source, solvent, and the addition of either metal salts or sensitizer did not affect this preferred order.

These results could be explained in terms of concerted 1-3, 1-5, and 1-7 sigmatropic rearrangements, although the mechanism of the reaction is still under investigation. With 1-(3,3-dimethylallyl)-, 1-acetoacetyl, and 1-(3,3-dimethylacryloyl)-indoles (Ij, Ik, Iℓ), however, the corresponding 3-substituted indoles (IIj, IIk, IIℓ) were obtained in 34.0%, 12.1%, and 21.5% yields, respectively, and 4- and 6-substituted indoles could not be isolated. This suggests homolytic cleavage of the N-C bond, followed by recombination of the generated radicals in a solvent cage, the unstable radicals being unable to undergo rearrangement to other positions other than the most reactive 3-position.

ii) 3-Substituted Indoles

With the 3-substituted indoles (Ig, Ih, Ii), rearrangement to the 3-position is blocked. Further, the increased steric hindrance due to the 3-substituent led to decreased yields of 4- and 2-substituted indoles, the 6-substituted indole being obtained as the major product.

iii) Indoles Substituted in the Benzene Ring

With the expectation that substituents in the benzene ring might change the preferred order of rearrangement, 1-acetyl-2-methyl-3-ethoxycarbonyl-5-methoxyindole (V) was irradiated, affording the 7-acetyl compound (VII) and the 6-acetyl compound (VI) in 15.3% and 36.0% yields, respectively.

II) Rearrangement of a Substituent connected through Sulfur

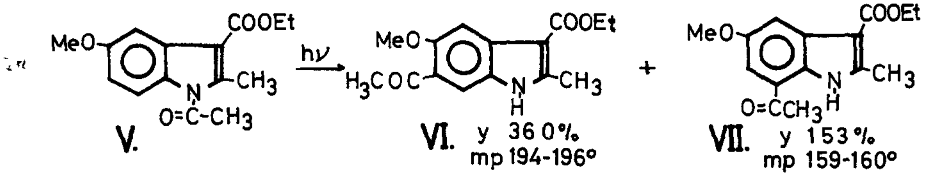
We expected that this photochemical reaction could also be applied to substituted indole derivatives in which the 1-substituent is connected to the ring through an element other than carbon, and this was confirmed by the following experiment.

Irradiation of 1-tosylindole (Ie) in ethanol with a Hanovia 450-W high-pressure mercury lamp resulted in the formation of 3-, 4-, and 6-tosylindole (IIe, IVe, IIIe) in 23.7%, 17.6%, and 1.6% yields, respectively.

III) Rearrangement of a Substituent connected through Oxygen

Similar rearrangement of methoxy and ethoxy groups was observed. Photolysis of 1-ethoxy-2-phenylindole (VIIIa) in methanol gave 2-phenyl-3-ethoxyindole (IXa, 11.5% yield), and a compound (XIa), mp 119.5-120.5°, containing an ethoxy group in the benzene ring, the position of substitution of which is still under investigation. Upon photolysis in ethanol, 1-methoxy-2-phenylindole (VIIIb) gave 2-phenyl-3-methoxyindole (IXb) in 17.8% yield, an unknown product (mp 145.5-146.5°) in 0.8% yield, and bis(2-phenyl-3-indolyl)methane (XII) whose methylene group was apparently derived from the methoxy moiety.

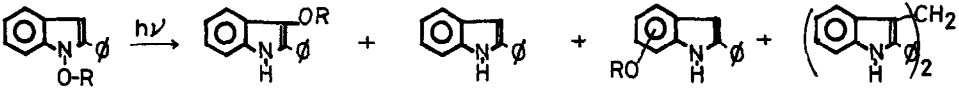
Satisfactory elemental analyses were obtained for all the compounds described here. Melting points are not corrected.



V.

VI. y 36 0% mp 194-196°

VII. y 15 3% mp 159-160°



VIII. a) R=Et	IX.	11.5 % 102-102.5°	X.	347 %	XI	3 4% 1195-1205°	XII.	—
b) R=Me		17 8 % 105-106°		190 %		—		5 2% 187-188°

unknown product (0.8% mp 145.5-146.5°) was isolated in the case of VIIIb.

REFERENCES

1. Presented in part at the 92th Meeting of the Pharmaceutical Society of Japan, Absts. Papers, p. 64 (M), 1972; 5th Symposium on Heterocyclic Chemistry (Japan) Gifu, 1972. Symposium Papers, p. 8.
2. O. Yonemitsu, S. Naruto, Tetrahedron Letters, 2297 (1971); Y. Ban, T. Oishi, Y. Sendo, S. Murakami, N. Unno, J. Kinoshita, T. Nakada, N. Shimizu, 3rd Symposium on Heterocyclic Chemistry (Japan), Tokyo, 1970. Symposium Papers, p. 43.
3. Photolysis was carried out under these conditions throughout the present study.