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PHOTO-INDUCED FRIEDEL-CRAFTS REACTIONS III. FORMATION OF INDOLEACETIC ACID

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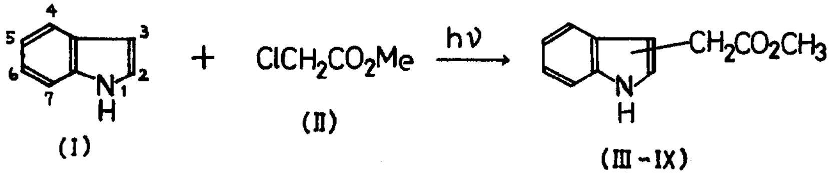
On photolysis of anisol or phenol with chloroacetamide, methoxy- or hydroxy-phenylacetamides were easily obtained.[1] This photo-induced Friedel-Crafts reaction has now been extended to indole series.

A 30 % aqueous methanol solution of indole (I)(10 mmole/l) with 3 equivalents of methyl chloroacetate (II) was irradiated with 500 W high pressure mercury lamp in nitrogen atmosphere. After 12 hr, the solvent was evaporated to leave an oil, which was mainly the mixture of seven isomeric methyl indoleacetates (III-IX). The separation of the mixture into their components was very difficult because of their similar chemical and chromatographic properties, however by repeated column chromatographies on silica-gel and alumina for several times it was accomplished. All seven esters were converted to their amides respectively. The isolation yields of this photo-reaction are shown in Table I.

Table I. Photo Friedel-Crafts reaction of indole with methyl chloroacetate

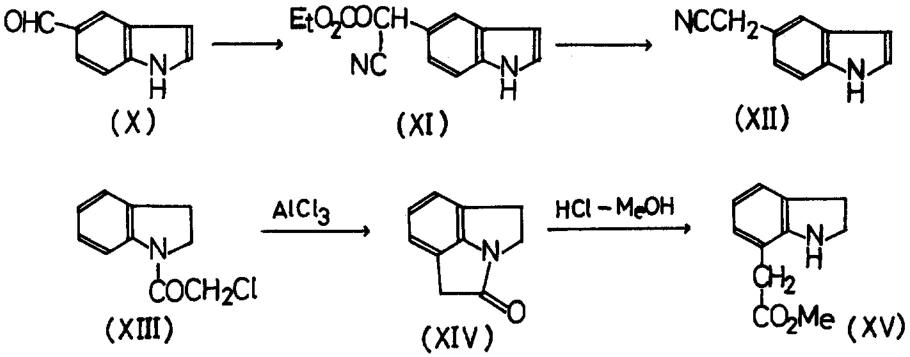
Reaction position	Product	Yield (%)	Spin density[a]
1	III	0.24	0.0914
2	IV	2.55	0.1679
3	V	1.35	0.2280
4	VI	6.20	0.2413
5	VII	0.13	-0.0054
6	VIII	1.69	0.1117
7	IX	1.9	0.1948

a: The spin density at each position of the radical cation of indole was calculated by SCF-MO method (Longuet-Higgins and Pople).[13]

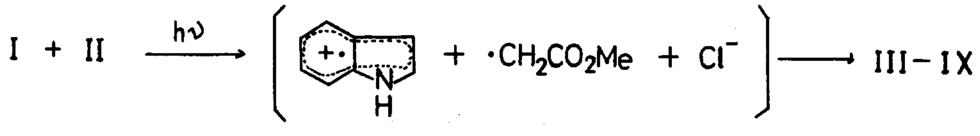


Indole with chloroacetamide gave photochemically the mixture of indoleacetamides, the sepatation of which was unsuccessful.

The structures of indole-1-, 2- and 3-acetic acid methyl esters (III-V) and their amides were easily confirmed by nmr spectroscopies. However, nmr spectra of benzene-substituted isomers are so similar to each other as to assign by the first order analysis. Therefor we synthesized all of seven isomers by unequivocal methods. Only indole-3-acetic acid methyl ester[2] and its amide[3] are known, however the known indole-1-[4], 2-[5] and 4-[6] acetic acids were easily converted to their derivatives. The indole-5- and 6-acetic acids were derived from corresponding indole aldehydes (X),[7] that is, the cyanhydrin derivatives (XI) of the aldehyds were reduced catalytically to indoleacetonitriles (XII), followed by alkaline hydrolysis. Methyl indole-7-acetate (IX) was reduced to the indoline (XV),[8] which was synthesized from N-chloroacetylindoline (XIII) by a convenient procedure; XIII was cyclized to 2-keto-1,2,4,5-tetrahydro[3,2,1,h,i]indole (XIV), followed by methanolysis to XV.



On the basis of the fluorescence quenching study by Hammond et al.[9] and the solvent effect study,[10] it was proposed that the photo-reaction of electron-rich aromatics with chlorinated amide groups in aqueous solution might be initiated photo-ionization of aromatic nucleus.[10] The flash-photolysis study of N-chloroacetyl-m-tyramine supported the mechanism,[11]



(XVI)

and the photo Friedel-Crafts reaction of indole with methyl chloroacetate may proceed as shown the above scheme.

If this were the mechanism, the reactivities of the positions on indole may depend on the electron spin densities[12] of the cation-radical (XVI) of indole. The calculated spin desities, which explain the high reactivity of 4-position of indole in this photo-reaction, by SCF-MO method[13] are shown in Table I.

Methyl indole-1-acetate (III) rearranged photochemically to the mixture of methyl indoleacetates by irradiation with 10 W low pressure mercury lamp. Indole-1-acetamide gave also similar results. As shown in Table II, the rearrangements to 6- and 3-positions of indole nucleus mainly occured, however we still have not any reliable calculation data, which interpret the high reactivity of 6-position.[14]

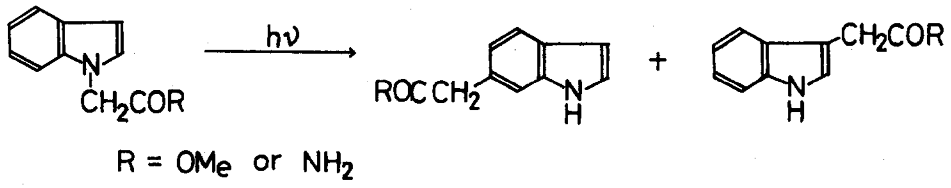
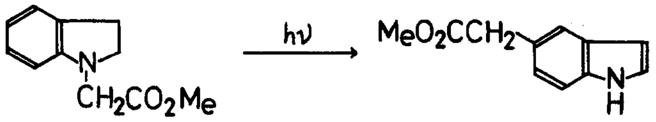


Table II. Rearrangement of methyl indole-1-acetate and indole-1-acetamide

Product	Yield (%) Me-ester	Yield (%) Amide
Indole	4.4	trace
Indole-1-acetic acid Me-ester or its amide	8.4	18.9
〃 -2- 〃	1.5	1.3
〃 -3- 〃	12.9	16.8
〃 -4- 〃	6.7	2.6
〃 -6- 〃	16.3	11.5
〃 -7- 〃	1.2	1.1

Finally, methyl indoline-1-acetate (XVII) was converted to methyl indole-5-acetate (VII), by a photochemical rearrangement to para-position of N-atom, in analogy with the photo-rearrangement of acetonitrile,[15] and a subsequent dehydrogenation reaction.



(XVII) (VII)

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