SYNTHESIS AND REACTION OF 2-ALLYLINDOLES

Ryuji Tachikawa, Atsusuke Terada, Kuniyuki Tomita and Teiki Iwaoka

CENTRAL RESEARCH LABORATORIES, SANKYO CO., LTD., SHINAGAWA-KU, TOKYO

Dedicated to Dr. S. Sugasawa, Professor Emeritus of the University of Tokyo, on his 80th birthday.

INTRODUCTION

A number of echinulin-type metabolite, containing a reversed isoprenic (1,1-dimethylallylic) chain in the 2-position of the indole nucleus have been isolated from moulds of the genus Aspergillus and some of them have been known to exhibit biological activities.[1)]

Synthesis of 2-allylindoles, especially 1,1-dimethylallylindoles, has been of interest in regard to the synthesis of the echinulins and many attempts have been made on this subject.

Recently we have found a convenient synthesis of 2-allylindoles by the application of the new reaction of indoles with succinimido-sulfonium salts developed by us.[2), 3)]

We will describe the studies on the synthesis of the 2-allylindoles, in the first section of this review.

On the other point of view, 2-allylindoles seem to be of potential

photochemical interest, since they have an isolated double bond and a hetero-aromatic ring bonded to a sp^3 carbon atom, in other word, a divinyl methane system.

Recently we found some attractive reactions of 2-allylindoles which proceeded via excited state, expectedly.[4] Recent studies on the photochemistry of 2-allylindoles in our laboratory will be presented in the second section of this review.

I) SYNTHESIS OF 2-ALLYLINDOLES

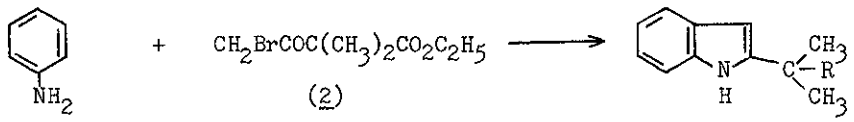
Two approaches toward the synthesis of 2-allylindoles have been reported;

(a) direct formation of the indole skeltons having allyl group or its precursors at the 2-position,

(b) insertion of allyl chain to the 2-position of the indole nucleus.

The first synthesis of 2-(1,1-dimethylallyl)indole (1) was carried out by the method (a) by Houghton and Saxton.[5]

Thus, Bischler reaction of ethyl 4-bromo-2,2-dimethylacetoacetate (2) with aniline gave ethyl indol-2-ylisobutyrate (3). Reduction of (3) with lithium aluminium hydride afforded the alcohol (4), which was then oxidized to the aldehyde (5) by acetic anhydride and dimethyl sulfoxide. Wittig reaction of the aldehyde with methylene triphenylphosphorane afforded (1) (eq 1).



(2)

(3) R= $CO_2C_2H_5$

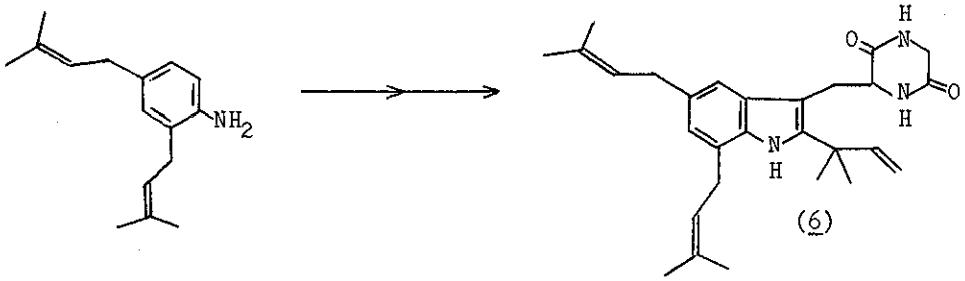
(4) CH_2OH

(5) CHO

(1) $CH{=}CH_2$

(eq 1)

The first total synthesis of echinuline (6) was performed by Y. Kishi and co-workers[6] by this procedure, starting from 2,4-di-(3,3-dimethylallyl)-aniline (eq 2).

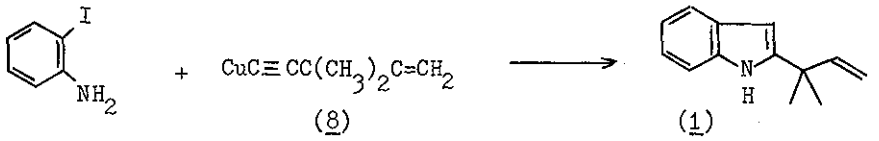


(6)

(eq 2)

Recently, Russell[7] reported a one step synthesis of (1) by the Bischler reaction using 1-bromo-3,3-dimethyl-4-penten-2-one, $CH_2BrCOC(CH_3)_2CH{=}CH_2$ (7).

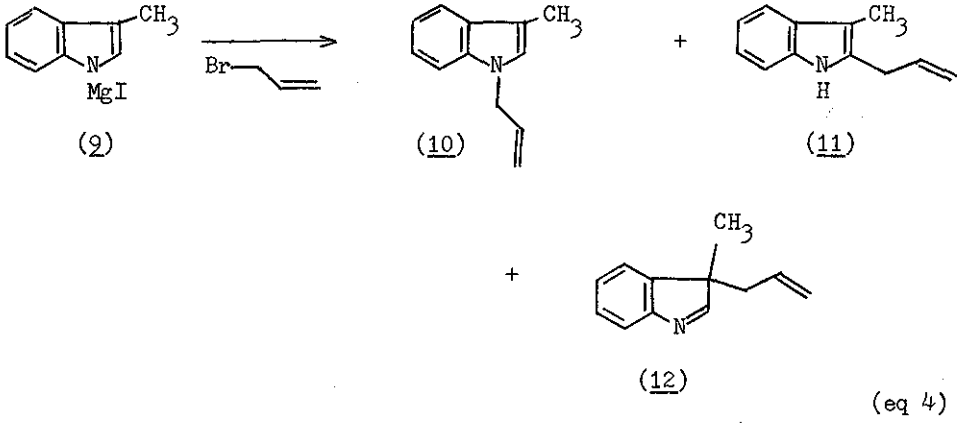
Plieninger and Sirowej[8] also reported another one step synthesis of (1) by the condensation reaction of o-iodoaniline and copper salt of 3,3-dimethyl-pent-1-en-4-yne (8) (eq 3).



(eq 3)

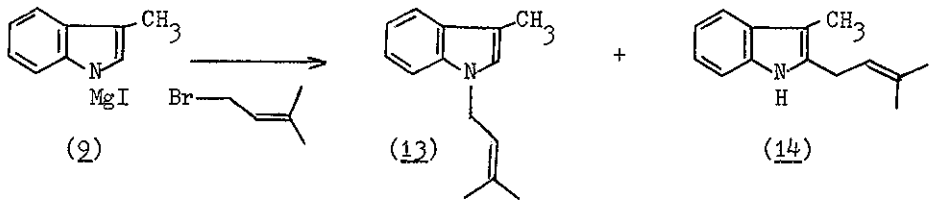
The insertion of the allyl chain in the 2-position of indoles (method b) has been much important in the standpoint of both the synthesis and biogenesis of the echinulins.

Jackson and Smith have investigated the reactions of some allylic halides with indole Grignard reagents.[9] 3-Methylindolyl magnesium iodide (9) reacted with allyl bromide to give a mixture of 1- and 2-allyl-3-methyl-indole, (10) and (11), and 3-allyl-3-methylindolenine (12). The formation of the 2-allylindole (11) was considered to proceed by the rearrangement of the initially formed indolenine (12) (eq 4).

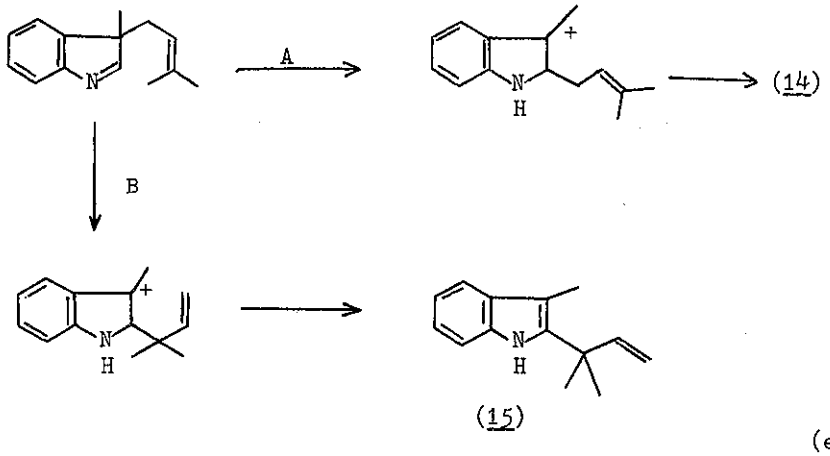


(eq 4)

3,3-Dimethylallyl bromide gave 1- and 2-allyl-3-methylindole (13) and (14) (eq 5). It was also suggested that the 2-allylindole (14) was formed via the 3-allylindolenine (not isolated) corresponding to (12), which implied the occurrence of the Wagner-Meerwein type rearrangement (A) rather than Claisen type reaction (B) since the desired 'inverted isoprenic' chain produce (15) has not been obtained (eq 6).



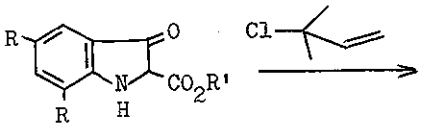
(eq 5)



(eq 6)

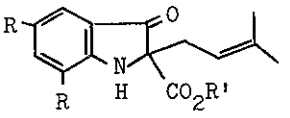
Plieninger and Sirowej[10] succeeded in the introduction of the allyl chain 'reversely' by the Claisen rearrangement of the indoxyl derivatives, although the 'normal' isoprenic chain was also introduced in some extent.

2-(Ethoxycarbonyl)indoxyl (15) reacted with 1,1-dimethylallyl chloride to give 2-ethoxycarbonyl-(3,3-dimethylallyl)-3-oxoindoline (16) and 2-ethoxycarbonyl-(1,1-dimethylallyl)-3-oxoindoline (17). The corresponding reaction with 5,7-dibromo-2-(methoxycarbonyl)indoxyl (18) yielded 5,7-dibromo-2-methoxycarbonyl-3-(3,3-dimethylallyloxy)indole (19) in addition to the C-alkylated products, (20) and (21). A Claisen type rearrangement of this allylether (19) led to the C-alkylated compound (21) (eq 7).



(15) R=H R'=C_2H_5

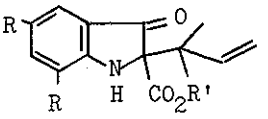
(18) Br CH_3



(16) R=H R'=C_2H_5

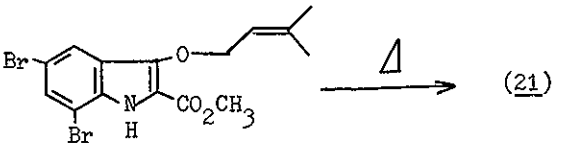
(2) Br CH_3

+



(17) R=H R'=C_2H_5

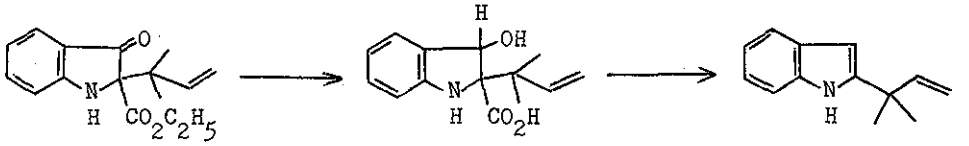
(21) Br CH_3



(19)

(eq 7)

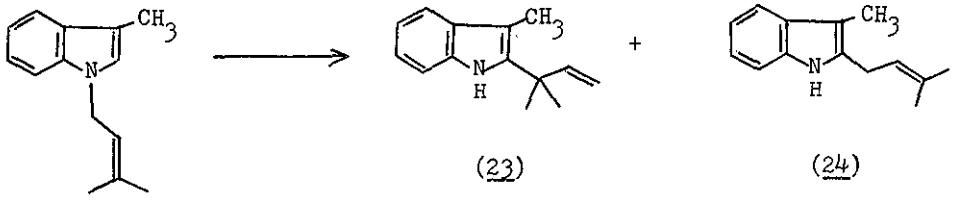
The compound (17) can be transformed into 2-(1,1-dimethylallyl)indole (1) by reduction with sodium borohydride followed by saponification, decarboxylation and dehydration (eq 8).[11]



(17) (1)

(eq 8)

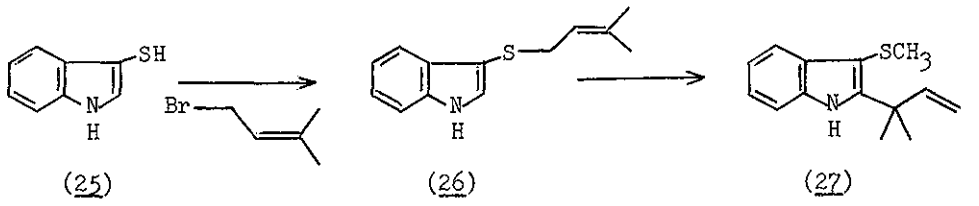
Casnati and Pochini[12] have studied the reactivity of N-(3,3-dimethylallyl)-3-alkylindoles as model systems in the biogenesis and synthesis of the echinulin-type compounds. An acid-catalysed rearrangement of the isoprene chain from the N- to the 2-position of the indole nucleus was observed, together with a partial rearrangement of the allyl chain. In this way, N-(3,3-dimethylallyl)-3-methylindoles (22) rearranged to 2-(1,1-dimethylallyl)-3-methylindole (23) and to 2-(3,3-dimethylallyl)-3-methylindole (24) (eq 9).



(22) (23) (24)

(eq 9)

Plieninger and co-workers reported thio-Claisen rearrangement in the indole series.[13] Reaction of 3-mercaptoindole (25) with 3,3-dimethylallyl bromide yielded 3-(3,3-dimethylallylthio)indole (26) along with some by-products. The reaction of (26) with methyl fluorosulfonate yielded 2-(1,1-dimethylallyl)-3-(methylthio)indole (27) (eq 10). Attempts to remove the 3-substituent of (27) were, however, unsuccessful.

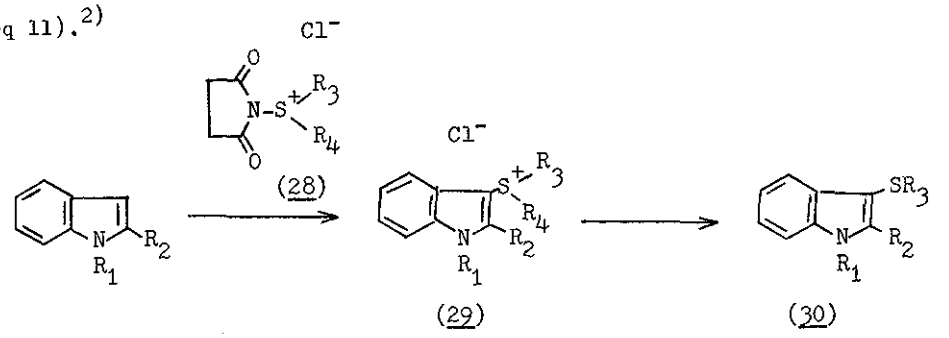


(25) (26) (27)

+ other products

(eq 10)

Recently we found that indole compounds reacted with succinimido-dialkyl- or alkylarylsulfonium chlorides (28) to give indole-3-sulfonium chlorides (29) which were converted to 3-alkylthio- or arylthioindoles (30) on pyrolysis (eq 11).[2]



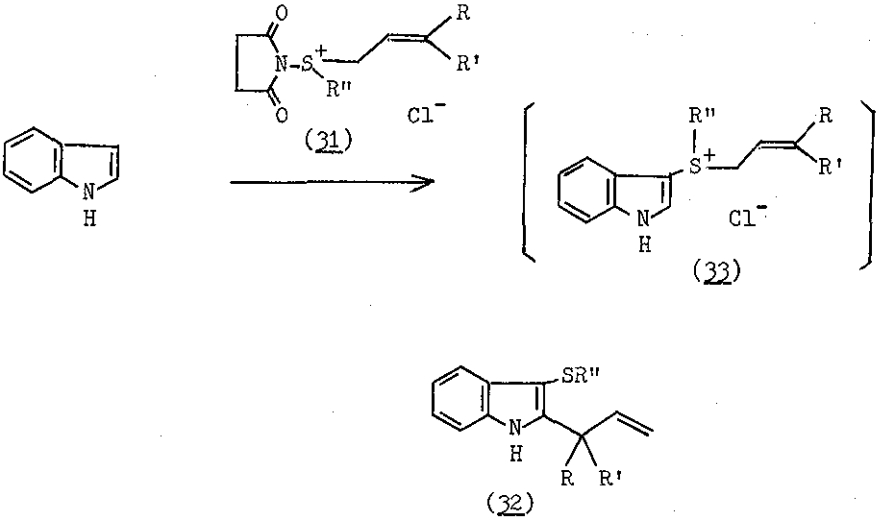
(28)

(29) (30)

R_1, R_2=H, alkyl R_3=alkyl, aryl R_4=alkyl

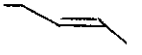
(eq 11)

When succinimido-diallyl or alkylallylsulfonium chlorides (31) were used, 2-allylindole-3-thioethers (32) were obtained as sole products. Thus, indole was added to a solution of succinimido-3,3-dimethylallylethylsulfonium chloride (31a), prepared from N-chlorosuccinimide and 3,3-dimethylallylethyl sulfide, in dichloromethane at -30°C. The temperature of the reaction mixture was raised gradually to 35°C during 1 hour. After removal of the solvent, 2-(1,1-dimethylallyl)-3-ethylthioindole (32a) was obtained in ca. 60% yield. Similarly, the reaction of some other diallyl or alkyl allyl sulfonium salts afforded 2-allyl-3-alkylthio- or 2-allyl-3-allylthioindoles (32b-e) in 40-60% yield (eq 12).

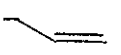


(31)(32)(33) a; R=R'=CH_3 R"=C_2H_5

b; R=CH_3 R'=H R"=C_2H_5

c; R=CH_3 R'=H R"= 

d; R=R'=H R"=C_2H_5

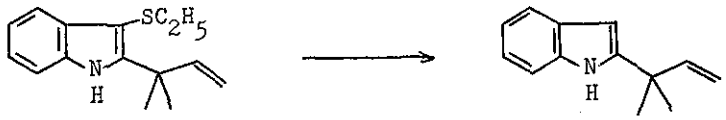
e; R=R'=H R"= 

(eq 12)

It is reasonable to consider that the allylindoles might be formed via sigmatropic rearrangement of the initially formed sulfonium salts (33), since analogous sulfonium salts (29) were isolated in the reaction of succinimidodialkylsulfoniumchlorides with indoles, as shown above.

It seems attractive that the rearrangement proceeds with complete reversal of the substituted allyl groups and no other products were obtained. These results provide a simpler and more efficient regio specific way to introduce allyl, especially 1,1-dimethylallyl chain in the 2-position of indoles.

Furthermore the reduction of (32a) with zinc powder in acetic acid at 60°C, 2-(1,1-dimethylallyl)indole (1) was obtained in good yield (eq 13). This is the first practical and the most convenient synthesis of (1) from indole.



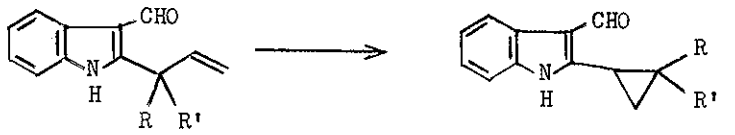
(32a) (1) (eq 13)

II PHOTOCHEMISTRY OF THE 2-ALLYLINDOLES

Photolysis of 2-(1,1-dimethylallyl)indole-3-carboxaldehyde (34), prepared from (1) by Vilsmeier reaction, in methanol or ethanol with a low pressure mercury lamp through quarz under nitrogen stream gave a crystalline product (35) in quantitative yield. The structure of the product was assigned to 2-(2,2-dimethylcyclopropyl)indole-3-carboxaldehyde on the basis of spectral data coupled with an elemental analysis.

On the contrary, irradiation of (1) caused no reaction and the starting material was recovered.

On the similar conditions, 2-(1-methylallyl)- and 2-allylindole-3-carboxaldehyde, (36) and (37), gave 2-(2-methylcyclopropyl)- and 2-cyclopropyl-3-carboxaldehyde, (38) and (39), respectively (eq 14). In these reactions, much decrease in the yield and apparent reaction rate have been observed with omission of the methyl groups in the α-position of the allyl substituents.



(34) R=R'=CH_3

(36) R=CH_3 R'=H

(37) R=R'=H

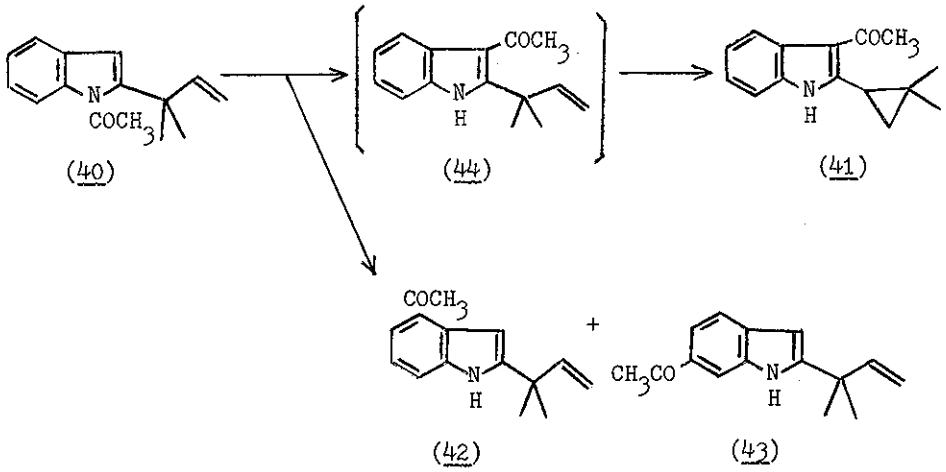
(35) R=R'=CH_3

(38) R=CH_3 R'=H

(39) R=R'=H

(eq 14)

Irradiation of N-acetyl-2-(1,1-dimethylallyl)indole (40) in methanol afforded 3-acetyl-2-(2,2-dimethylallylcyclopropyl)indole (41) as the main product along with 4- and 6-acetyl-2-(1,1-dimethylallyl)indole (42) and (43) as minor products (eq 15). It seems likely that the compound (41) was formed via 3-acetyl-2-(1,1-dimethylallyl)indole (44) initially formed, since N-acyl-2-alkylindoles have been known to afford 3-acyl-2-alkylindoles mainly, accompanied with 4- and 6-acylisomers on photolysis.[14]

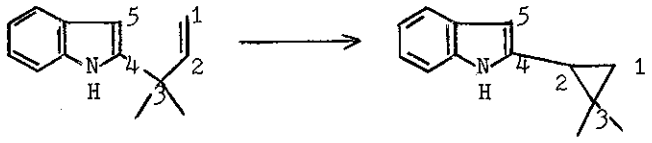


(40) (44) (41) (42) (43)

(eq 15)

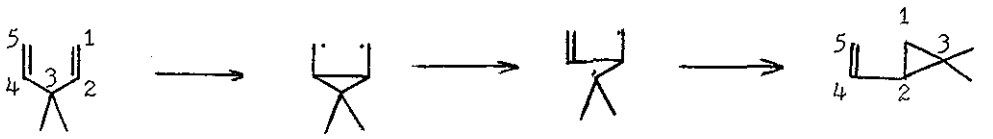
These observations suggest that the carbonyl functions in the 3-position of the 2-allylindoles appear to play a critical role in the transformation of the 2-allyl chain into the cyclopropyl ring.

The formation of the 2-cyclopropyl compounds formally involves the migration of the indole skeleton bonded to the saturated carbon, C-3, to C-2 of the vinyl moiety, and concomitant three membered ring formation between C-3 and C-1, as depicted below, which is reasonably explained by the divinyl methane rearrangement (eq 16).[15]



(eq 16)

It was noted by Zimmerman and co-workers[15] that the skelatal change in the divinyl methane rearrangement could be accounted for by one basic mechanism, as shown in eq 17.



(eq 17)

The increase of the reactivity brought about by the gem-dimethyl groups at the 2-allyl groups, as described before, is likely a manifestation of the well known Thorpe-Ingold effect and also could be ascribed to the added stabilization of the odd-electron density developing at C-3 by the methyl groups.

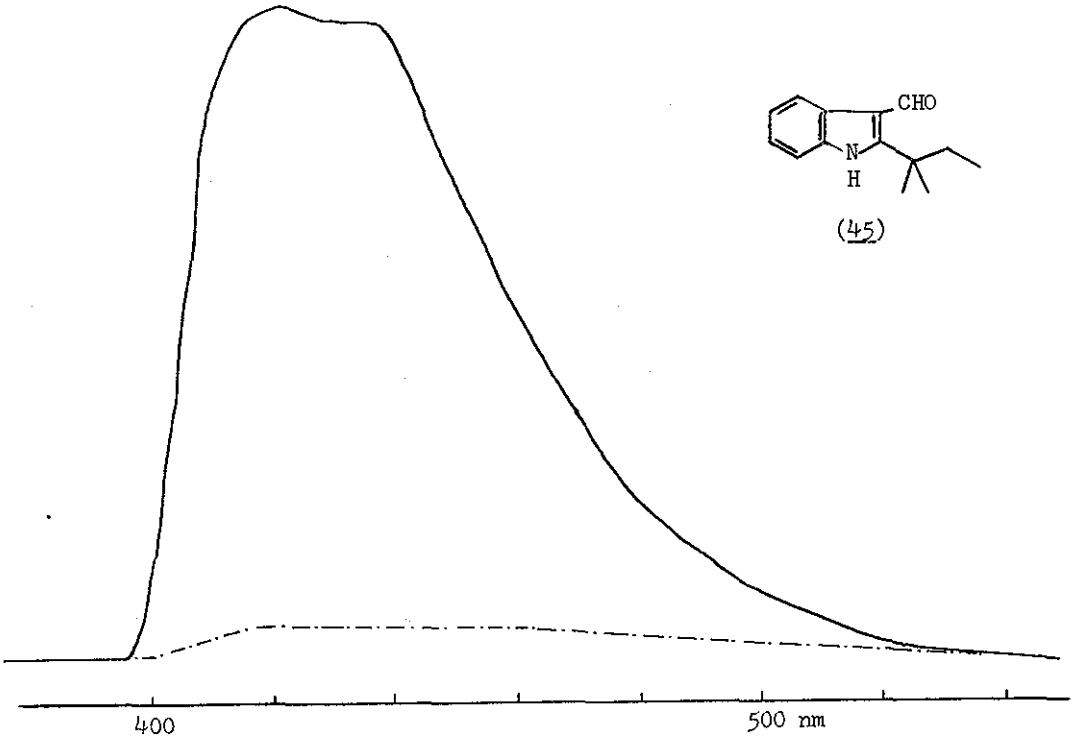
To elucidate the characters of the excited state contributed in this reaction, some mechanistic studies have been made.

Sensitizing experiments using a triplet sensitizer (benzophenone, E_T 68.5 Kcal/mol, 418 nm) showed much effect suggesting that the triplet multiplicity is required for the rearrangement.

The UV spectrum of the compound (34) and its dihydro product (45) is almost identical, which makes clear that there exist no electronic interaction between the indole skeleton itself and the vinyl moiety in the ground state.

On the other hand, the phosphorescence spectra of them showed a characteristic feature; they showed similar emission spectra in shape but the dihydro compound (45) exhibits more than 30 times strong emission in intensity than (34) (fig 1).

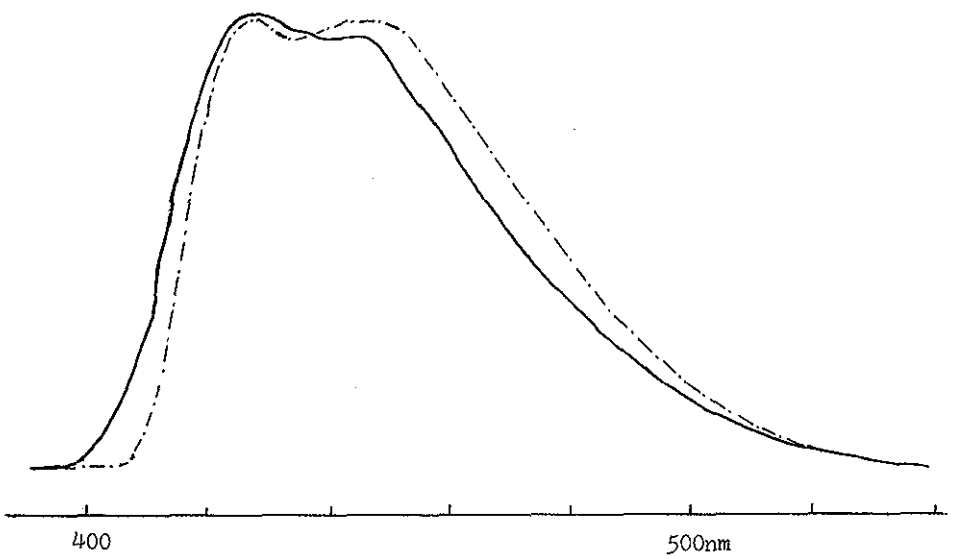
These results indicate that the phosphorescence of the indole skeleton of (34) is quenched by the terminal olefine, which suggests the presence of the interaction between the indole and the vinyl function in the triplet state, that is, the intramolecular exciplex seems to be formed though the exact mechanism is still not completely elucidated.



(45)

(fig 1) Phosphorescence spectra of (45)(———) and (34)(-·-·-·) in EPA at 77°K with the excitation at 310 nm.

The apparent phosphorescence life time of (34) in EPA at 77°K was estimated to ca. 0.16 sec. The relatively short life time is indicative of the significant role of n-π^* state in this molecule, which was also supported by the solvent effect, observed in the emission spectra (fig 2), though complete evidences are lacking.



(fig 2) Phosphorescence spectra of (34) at 77°K with the excitation at 310 nm in EPA(———) and methylcyclohexane(·—·—·).

Table 1, obtained by Song and Kurtin,[16] exhibits that indole which has no carbonyl substituents at the 3-position possesses relatively low phosphorescence quantum yield in comparison with that for fluorescence and that, on the other hand, the carbonyl substituted compound have high phosphorescent efficiency.

These data would explain the differences of the photochemical reactivities between the compound (1) and (34), since a significant role of the phosphorescent state have been established in the latter case.

(table 1) The relative luminescence yields relative to indole in EPA at 77°K and the ratios of the phophorescence to fluorescence yields.

	ϕ_f	ϕ_p	ϕ_p/ϕ_f
Indole	1.00	1.00	0.37
Indole-3-carboxaldehyde	0.07	1.75	10.00

According to Zimmerman,[15] the divinyl methane rearrangement has been known to arise from the singlet manifold when the molecule has a nonconstrained free π moiety and the triplet reaction proceeds only when constrained non free π moiety presents. This structure-multiplicity relationship rule is generally accepted as 'free roter effect'.

Present rearrangement observed in the indole series which proceeds via triplet state, despite of the presence of the 'free π moiety', seem to provide a new type of photochemical reaction.

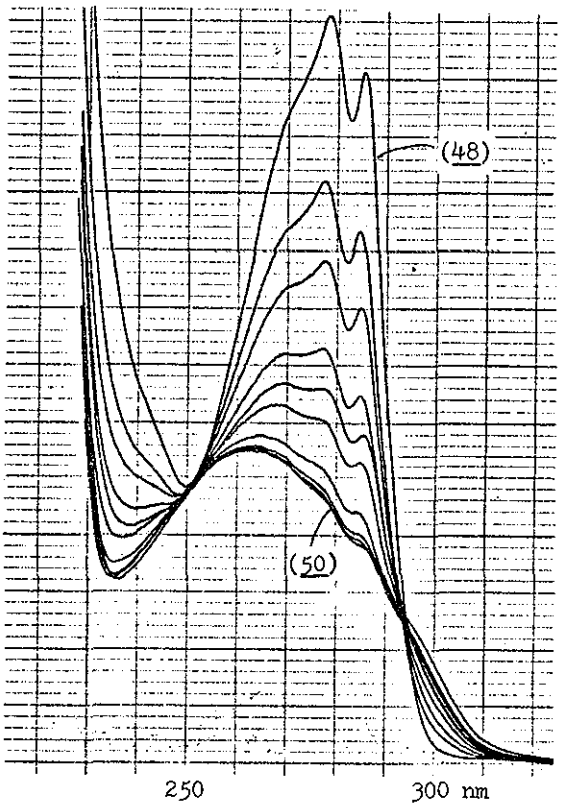
Thus, it was found that the photochemical reactions of the 2-allylindoles were much effected by the 3-carbonyl groups. Then the photochemical behaviors of the 2-allylindoles with other substituents at 3-position were examined.

Irradiation of 2-(1,1-dimethylallyl)indole-3-aldoxime (46) gave a equilibrium mixture of the geometrical isomers of syn- and anti-oximes, (47) and (46) (eq 18).

(46) (47)

(eq 18)

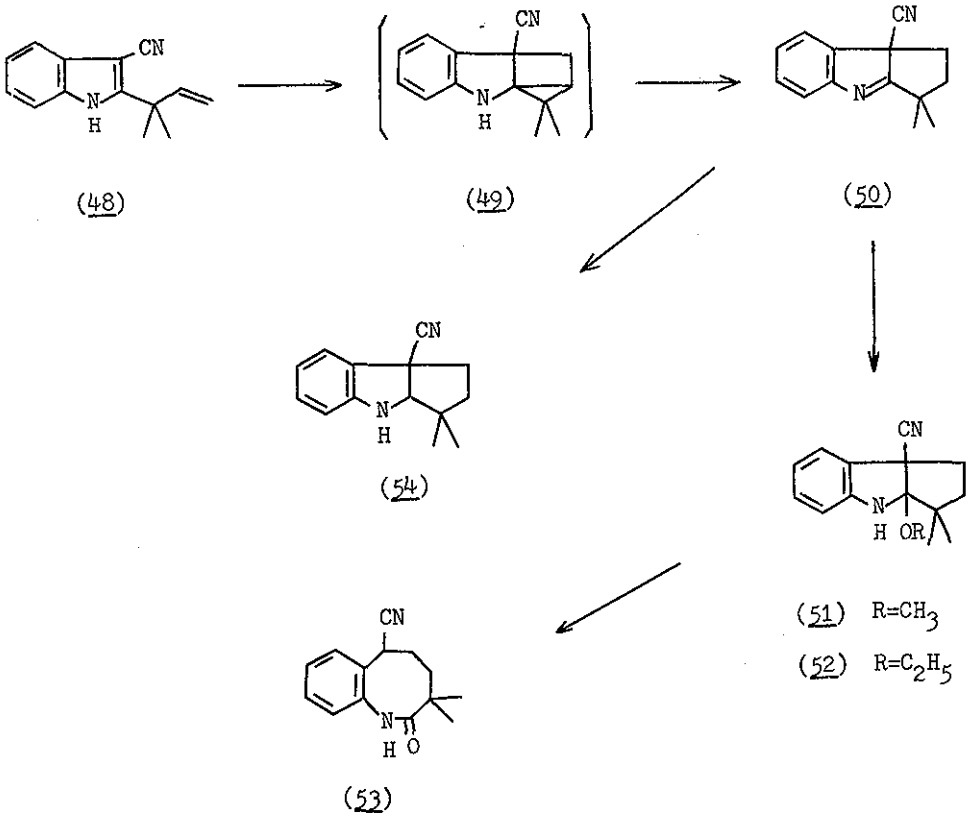
Photolysis of 2-(1,1-dimethylallyl)-3-cyanoindole (48) in methanol with low pressure mercury lamp gave an oily product in quantitative yield and the structure was assigned as the indolenine (50). Figure 3 shows the time dependent changes of the UV spectra during irradiation, which indicates the reaction proceeds simply and quantitatively.



(fig 3)
UV spectral change of (48) observed during irradiation in MeOH.

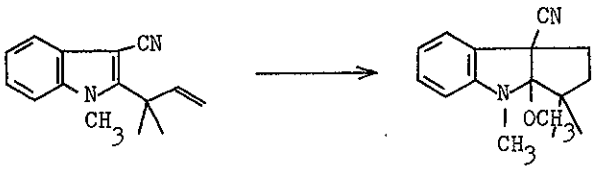
The product (50) was not stable and prolonged heating in ROH gave corresponding alkoxy-indolenine (51) and (52), in quantitative yields.

When the compounds (51) and (52) were heated in alcoholic KOH solution, the benzazocine (53) was obtained in good yield. On the other hand, treatment of (50) with sodium borohydride or irradiation of (48) in the presence of sodium borohydride gave the indoline (54) quantitatively. These reactions provide novel ring transformations of the indole nucleus (eq 19).

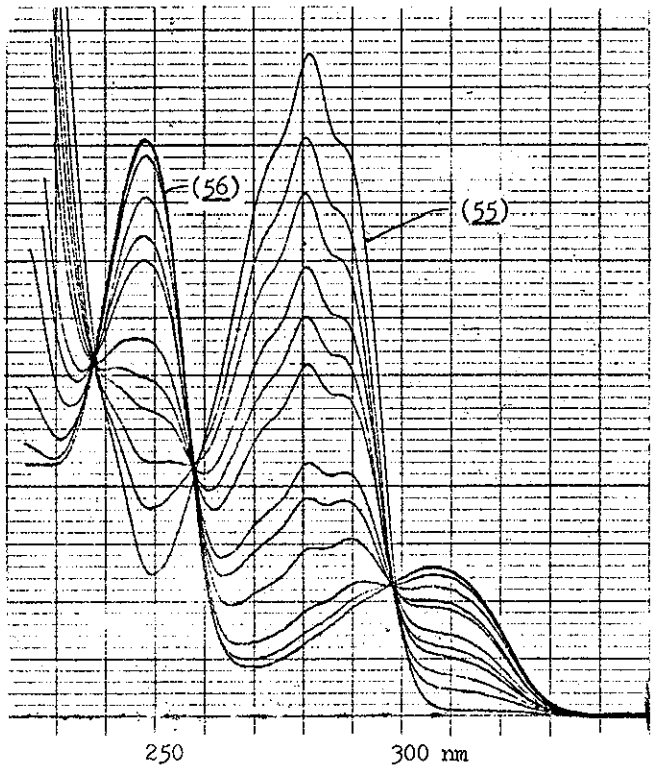


(eq 19)

Irradiation of N-methyl-2-(1,1-dimethylallyl)-3-cyanoindole (55) in methanol afforded the alkoxy-indoline (56) quantitatively (eq 20). In this case, the intermediate indolenium compound corresponding to (50), which seemed to be highly reactive, was not isolated. Figure 4 exhibits clearly the direct formation of (56).

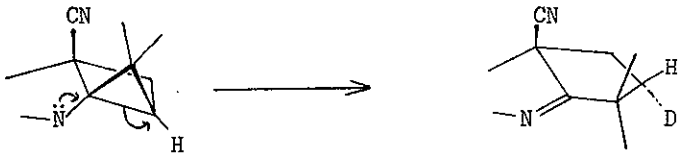


(55) (56) (eq 20)



(fig 4)
UV spectral change of (55) observed during irradiation in MeOH.

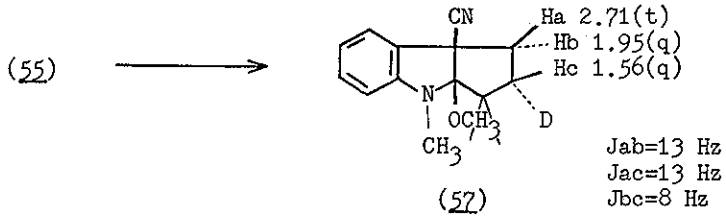
It seems reasonable to assume that the compound (50) might be formed via (2+2) cycloaddition of the terminal olefine with the indole ring and subsequent isomerization of the cycloaddition product (49). If it would be correct, when irradiated in MeOD instead of MeOH, D atom will be introduced stereoselectively in the beta side of the cyclopentyl part, as shown in fig. 5.



(fig 5)

Therefore, the compound (55) was irradiated in MeOD and the product (57) which had one mass unit larger molecular ion peak in mass spectrum than (56) was obtained quantitatively. The NMR spectrum of (57) was found to be fairly simple in contrast to that of (56) and was assigned as shown in eq 21.

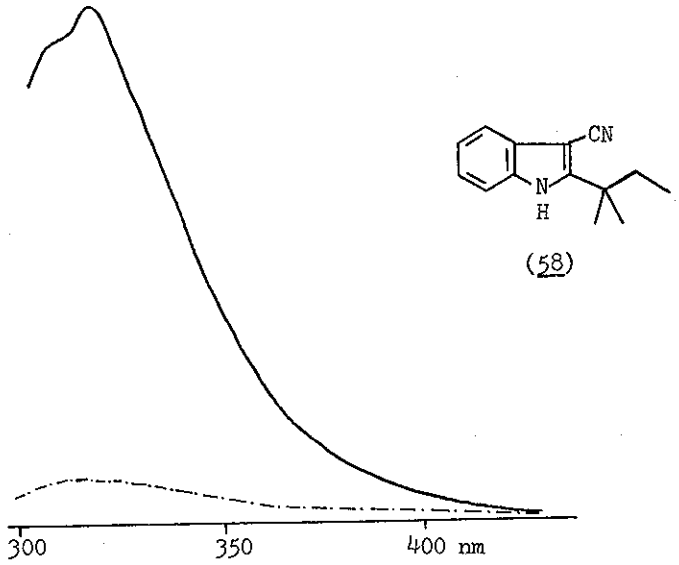
These facts suggest that the reaction proceeds stereoselectively as expected and would support the intermediacy of the assumed addition product (49).



(eq 21)

In order to obtain further informations in the primary state of the reaction, additional experiments were performed.

Triplet sensitization of (48) gave no sign of (50). Thus the reaction appears to proceed from the singlet state. Furthermore, much decrease in emission intensity was observed in the fluorescence spectrum of (48) comparing with that of the dihydro compound (58) (fig 6). (A charge-transfer complex between the indole skeleton and the terminal olefine in the ground state is not formed, since the UV spectra of (48) and (58) are identical).



(58)

(fig 6) Fluorescence spectra of (48)(·—·—·) and (58)(———) in n-hexane.

These results demonstrate that the fluorescence of the indole ring of (48) is quenched by the terminal olefin which suggests the formation of intramolecular exciplex in the singlet state.

In summary, it has become apparent that the photochemical reactivities of the 2-allylindoles were dependent on the substituents at 3-position. The extensive studies to elucidate the scope and utility of these reactions are now in progress.

REFERENCES

1) G. Casnati, A. Pochini and R. Ungaro, Gazz. chim. ital., 103, 141 (1973).
A. Dossena, R. Marchelli and A. Pochini, Chem. Commun., 1974, 771.
H. Itokawa, Y. Akito and M. Yamazaki, J. Pharm. Soc. Japan, 93, 1251 (1973).
R. Cardillo, C. Fuganti, G. Gatti, D. Ghiringhelli and P. Grasselli, Tetrahedron Lett., 1974, 3163.
P. S. Steyn, Tetrahedron, 29, 107 (1973).
P. M. Scott, B. P. C. Kennedy, J. Harwig and Y. K. Chen, Appl. Microbiol., 28, 892 (1974).
A. Dossena, R. Marchelli and A. Pochini, Experientia, 31, 1249 (1975).
T. Hamasaki, K. Nagayama and Y. Hatsuda, Agr. Biol. Chem., 40, 203 (1976).
H. Nagasawa, A. Isogai, K. Ikeda, S. Sato, S. Murakoshi, A. Suzuki and S. Tamura, Agr. Biol. Chem., 39, 1901 (1975).
H. Nagasawa, A. Isogai, A. Suzuki and S. Tamura, Tetrahedron Lett., 1976, 1601.
2) K. Tomita, A. Terada and R. Tachikawa, Heterocycles, 4, 729 (1976).
3) ibid., 4, 733 (1976).

4) Presented at the 9th Congress of Heterocyclic Chemistry, Fukuoka, Japan, 1976; K. Tomita, T. Iwaoka and T. Terada, reprints p 6.

5) E. Houghton and J. E. Saxton, J. Chem. Soc. (C), 1969, 595.

6) N. Takamatsu, S. Inoue and Y. Kishi, Tetrahedron Lett., 1971, 4665.

7) R. A. Russell, Aust. J. Chem., 28, 2535 (1975).

8) H. Plieninger and H. Sirowej, Chem. Ber., 104, 2027 (1971).

9) A. H. Jackson and A. E. Smith, Tetrahedron, 21, 989 (1965).

10) H. Plieninger, H. Sirowej and D, Rau, Chem. Ber., 104, 1863 (1971).

11) ibid., 1869 (1971).

12) G. Casnati and A. Pochini, Chem. Commun., 1970, 1328.

13) H. Plieninger, H. P. Kraemer and H. Sirowej, Chem. Ber, 107, 3915 (1974).

14) M. Somei and M. Natsume, Tetrahedron Lett., 1973, 2451.

15) A comprehensive review is available: S. S. Hixson, P. S. Mariano and H. E. Zimmerman, Chem. Rev., 73, 531 (1973).

16) P. S. Song and W. E. Kurtin, J. Amer. Chem. Soc., 91, 4892 (1969).

Received, 25th July, 1977