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Study on the Reactions of the Side Chains of Azulenes[†]

Kouichi SATOH*

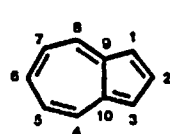
Abstract

Activations of side chains in azulenes were tried by various methods. When the 3-position of these compounds were substituted for acyl groups, condensations occurred owing to activation of methyl group at the 4-position. Aceheptylenes could easily be synthesized from 3-formylguaiazulene through this reaction. In the case of alkylazulenes like 3-alkylguaiazulenes to which the method can not be applied. However, with a strong electrophilic reagent such as the Vilsmeier reagent, not only its methyl group at the 4-position but also isopropyl group at the 7-position could be activated and the products from side chain reactions were obtained. For structural analysis of the products from these reactions, a calculation method was also derived for obtaining an approximate δ value in ¹³C-NMR spectrum, which will be explained later.

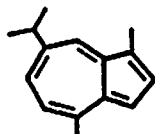
1. Introduction

Azulene (A)¹⁾ is a none-benzenoid aromatic compound with blue color, with contain a pentacyclic and a heptacyclic rings. Azulenes are consist of the compounds with various color corresponding to the kinds of substituents and the position of substitution. Azulenes have become to attract attention for their antiphlogistic effect (for swelling on tunica mucosa laryngist etc.) and antiulcer effects with a mild and slight side effect. Therefore, they are now widely used as medicines.^{††}

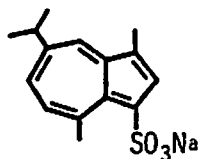
Among them, guaiazulene (1) and its sodium sulfonate derivative (B) are ones being manufactured in the highest amount.



Azulene (A)



Guaiazulene (1)



(B)

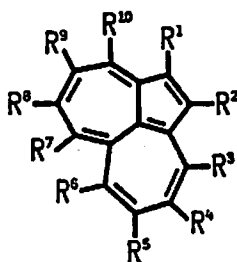
Diacetylene derivatives²⁾ of azulene and aceheptylenes³⁾ (C), which is one of azulene derivatives, are used as a data medium for tracking optical recording disc (the whole data of "Kohjien" can be recorded in a sheet of this disc), since they have a characteristic of

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† This paper is an epitome of the dissertation for which the author received a doctorate in engineering from Meiji University on March 25, 1989.

†† Azulens for medical pupose are used as toroch and gastrointestinal medicines both of which have pale green color.

strong selective absorption for semiconductor laser.



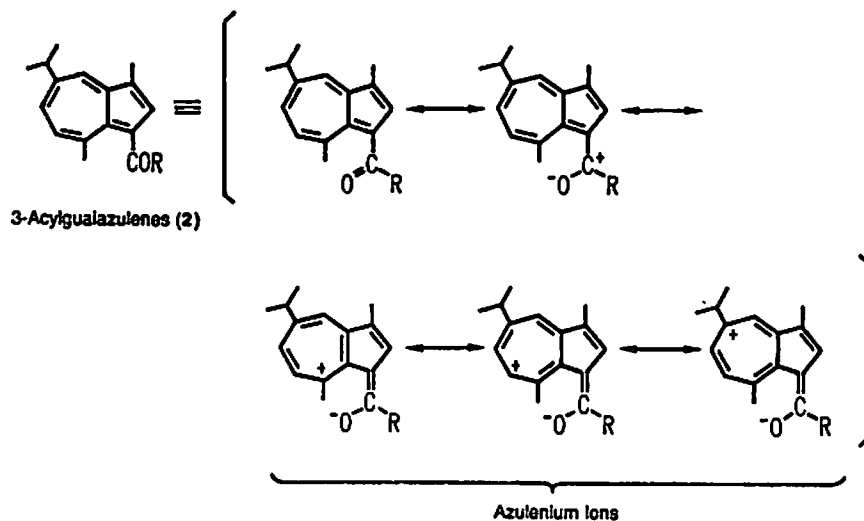
Aceheptylene compounds (C)

These examples show an increasing importance of azulene derivatives in the industries of medicines and optical data medium. However, synthesis reactions of azulene derivatives have scarcely been studied so far except that of electrophilic substitutions.⁴⁾ New kinds of azulene derivatives are now socially needed and accordingly, studies of synthesis reactions besides substitution will be required. The author took up 7-isopropyl-1,4-dimethylazulene which the formal name for guaiazulene (1) and the only commercial product manufactured for market, and studied on reactions of its side chain for the purpose of developing new methods for synthesis of azulene derivatives. As a result, a method to activate the side chains of azulenes and consequently through this activation method a new route to synthesize aceheptylene compounds mentioned above in a good yield, which is now used for optical recording medium, were developed.

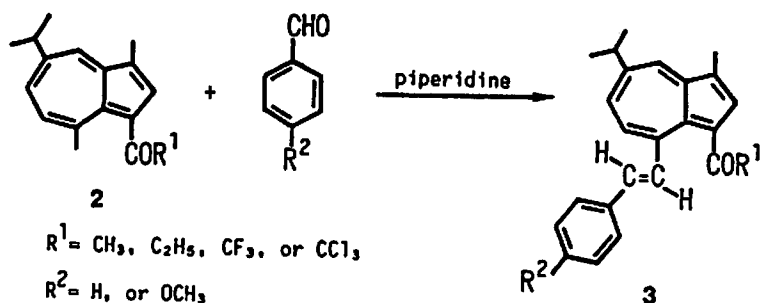
2. Reactions of the methyl group at the 4-position of 3-acylguaiiazulenes⁵⁾

Azulene is structural isomer of naphthalene and is quantitatively transformed to the latter when it is heated at over 350°C in a vacuum.⁶⁾ The chemical properties of azulene are also very similar to those of naphthalene. However, azulenes has a relatively high dipole moment value of 1 D⁷⁾ (which is nearly the same as that of chloroform) as the result of polarization with negatively charged pentacyclic and positively charged heptacyclic rings (azulenium ion structure). In case of 1, however, the contribution of azulenium ion structure to resonance is considered not to be large enough to activate the side chain of the heptacyclic ring (the methyl group at the 4-position and the isopropyl group at 7-position). Accordingly, taking these considerations into accounts, the author adopted the following idea of mechanism for activated side chains. The methyl group at the 4-position will possibly be activated if an electron attractive group with unsaturated bond such as acyl group is substituted at the 3-position of 1 and consequently the contribution of azulenium ion structure is increased.

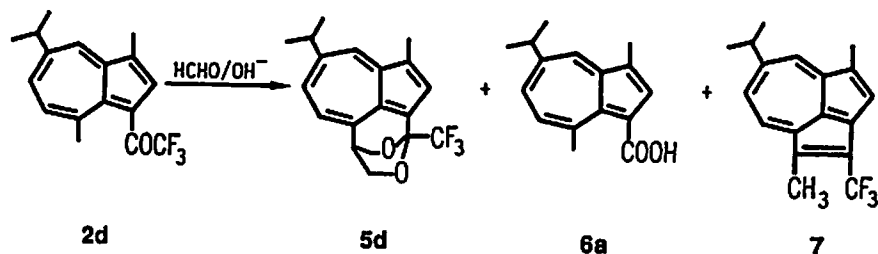
So, arylaldehydes were allowed to react with 3-formylguaiiazulene⁸⁾ (2a), 3-acetylguaiiazulene (2b) and 3-propionylguaiiazulene (2c), respectively and the condensation products with methyl group at the 4-position (3) were obtained from each reactions. When formaldehyde was made to react with 2, only 2a and 3-trifluoroacetylguaiiazulene (2d)



reacted with methyl group at 4-position, which gave dioxane compounds (5a) and (5d) which are products resulted from the reaction with 2 moles of formaldehyde.



The reactions of 3-alkylguaiazulenes (4), in which the methyl group at 4-position is not considered to be activated, from their resonance structures, with arylaldehyde and formaldehyde were not observed at all. By the way, a cyclopenta[*c,d*]azulenes was obtained as a by-product from the reaction of 2d with formaldehyde, which suggested a possibility of synthesizing polycyclic compounds from 2.

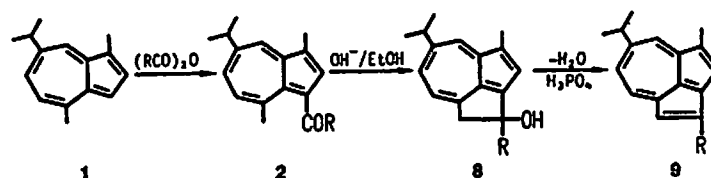


3. Synthesis of polycyclic compounds

3.1 Ring-closing reaction of 3-trifluoroacetyl-4-methylguaiazulene⁵⁾ (2d)

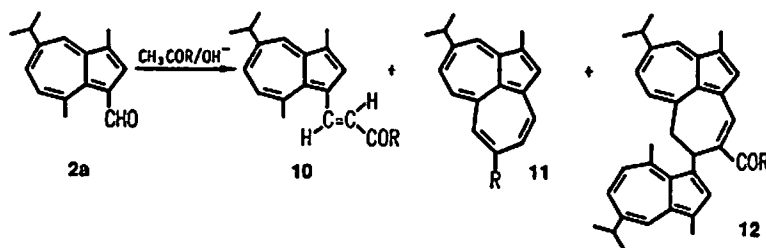
When 2d was treated with ethanolic NaOH solution, a ring-closed product (8d) was obtained. Dehydration of this product with phosphoric acid gave cyclopenta[*c,d*]azulenes

(9d). Besides, ring-closed products (8e), (8f) and cyclopenta[*c,d*]azulene (9e) were given from the same reaction of 3-pentafluoropropionylguaiazulene (2e) and 3-heptafluorobutylguaiazulene (2f). However, as for 2a-2c, any reactions could not be observed at all.



R	Yield (%)			
	2	8	9	
d	CF ₃	68	34	23
e	C ₂ F ₅	94	59	97
f	C ₃ F ₇	87	52	-

The same treatment of 3-trichloroacetylguiazulene (2g) with ethanolic NaOH solution gave 3-carboxylic ethyl derivative (8c) and 3-carboxylic derivative (6a). When methanol or propanol was used as solvent instead of ethanol, the corresponding 3-carboxylic ester (6b) or (6d) was formed. However, 2-propanol or 2-methyl-2-propanol was adopted as solvent, only 6a was given. And when 2d was made to react in the latter solvents, only 6a was given and the formation of ring-closed product (8d) was not observed.⁹⁾



R	Yield (%)			
	10	11	12	
a	CF ₃	trace	3	82
b	CH ₃	28	39	6
c	C ₂ H ₅	55	17	18
d	CH(CH ₃) ₂	51	2	47
e	C(CH ₃) ₃	86	5	0
f	C ₆ H ₄ OCH ₃	16	6	0

From these results, it was estimated that alcohol's addition to carbonyl carbon atoms is closely related to ring-closed reactions. Assuming this, the reaction paths were discussed.

3.2 Synthesis of aceheptylenes from 3-formylguaiazulene¹⁰⁾ (2a)

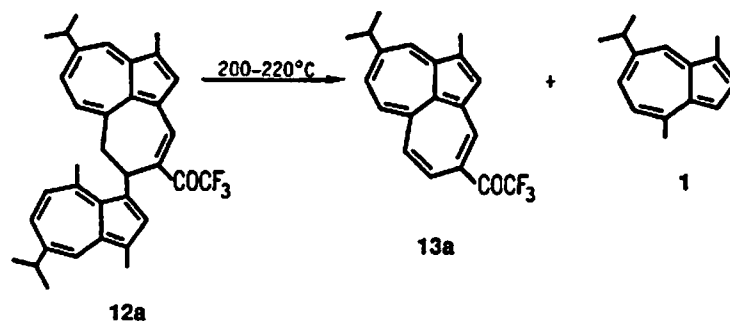
Aceheptylenes are now manufactured by the synthesis method of Hafner *et al*¹¹⁾. However, since it involves various steps in its synthesis process, the yield is relatively low. Besides, the raw material chemicals are rather expensive. Consequently, it is not necessarily profitable for the method of industrial manufacturing. If the 3-position of 1 is substituted for trifluoroacetylvinyl group which is vinilogue of trifluoroacetyl group, and the synthesis

method of cyclopenta[*c,d*]azulenes mentioned above is applied, aceheptylenes were expected to form through ring-closing dehydration in much the same way as 2d. On this assumption, 2a and 1,1,1-trifluoroacetone (TFA) were made to react in ethanol in the presence of NaOH catalyst. As a result, three kinds of products were obtained: 3-trifluoroacetylvinylguaiazulene (10a), aceheptylenes (11a) and a by-product (12a). Ring-closed products like 8d were not found among the products. However, after the formation, 10a was assumed to have condensed to a ring-closed dehydrated structure.

The reactions of 2a with various methyl ketones such as acetone, methyl ethyl ketone, 2-methyl-3-butanone, pinacolone, and acetophenone gave the corresponding aceheptylenes (11b)-(11f), respectively.

Though the yield was only 1%, aceheptylenes were obtained from the reaction of 2a with diethyl ketone, and cyclohexanone, both of which have methylene groups activated.

A by-product 12a, which is formed by the condensation of 2 moles of 2a and 1 mole methyl ketone, was found among the products of the reaction of 2a with TFA, acetone, methyl ethyl ketone, and 3-methyl-2-butanone. A by-product 12a was also given from the reaction of 10a with 2a in ethanolic NaOH solution. From those results, the formation of aceheptylenes 11 and by-products 12 proved to be a competitive reaction.



In order to increase the yield of 11, the reaction conditions were examined again. But the formation of 12 could not be controlled.

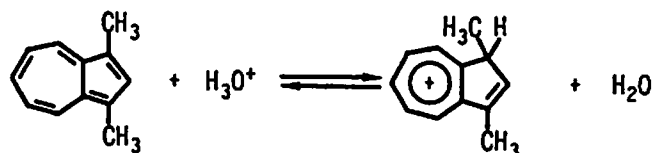
From those facts that 12 is dihydroaceheptylenes and that it has a marked peak of 1 in the mass spectra, 11 was expected to yield on pyrolysis. On this assumption, when 12a was heated at 200-220°C, 13a was obtained in a yield of 33%. Through these reactions, it has become possible to synthesize aceheptylenes in a considerably high yield, which is now used as materials for optical recording medium.

4. The Vilsmeier reaction of 3-alkylguaiazulenes^{12,13)}

It was confirmed in a previous section 2 that the side chain of 3-alkylguaiazulenes (4) are not activated. When 1,3-dimethylazulene is dissolved in an acid, a proton is added at the 1-position to form azulonium ion.

Similarly, if addition of an electrophilic reagent on the pentacyclic ring in 4 occur, an azulonium ion will be formed and consequently the side chain will be activated. The

Vilsmeier reagent, a strong electrophilic reagent, reacted with 4 to gave side chain reaction products.



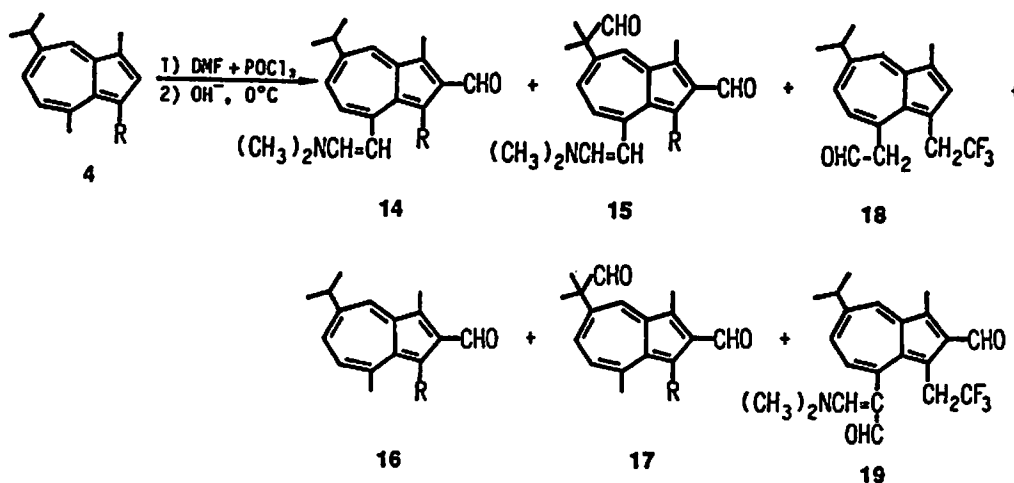
1,3-Dimethylazulene

4.1 The Vilsmeier reaction of guaiazulene (1)

To begin with, whether the Vilsmeier reaction is effective on the acylation of azulenes was examined. The Vilsmeier reaction is an effective method for the formylation of aromatic compounds, but examples for synthesizing ketones by this method have hardly been reported. When 1 was allowed to react with *N,N*-dimethylformamide (DMF) and phosphorous oxychloride (POCl_3), 2a was given in good yield. Similarly, the reaction of 1 with *N,N*-dimethylacetoamide- POCl_3 or *N,N*-dimethylpropionamide gave 2b and 2c, respectively. When the Friedel-Crafts reaction was compared with the Vilsmeier reaction with respect to the yields of 2b and 2c, it was proved that the latter is of greater advantage for synthesizing acylazulenes than the former (The latter give 2b and 2c in a yield of twice and four times high as those given by the former, respectively).

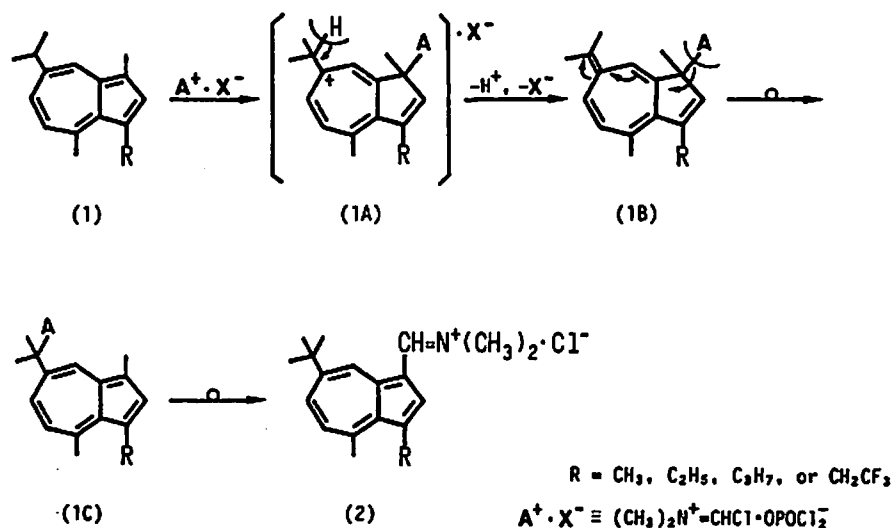
4.2 The Vilsmeier reaction of 3-alkylguaiazulenes (4)

In the following four kinds of 4 including 3-methylguaiazulene (4a), 3-ethylguaiazulene (4a), 3-ethylguaiazulene (4b), 3-propylguaiazulene (4c), and 3-(2,2,2-trifluoroethyl) guaiazulene (4d), π -electron density is the highest at 1- or 3-position, followed by the 2- or 5-position. Therefore, on the Vilsmeier reaction with DMF- POCl_3 , formylation of 4 is expected to occur at the 2- or 5- position. However, the resultant products were 6 in kinds at the highest in those reactions. Among them, products resulted from the reaction of the methyl group at the 4-position were included.



All of these products were obtained by a mild hydrolysis. The chiefly compounds of

these products were 14a, 14b and 14c or 15d, which were basic mono- or diformyl derivatives, accompanied by 2-formyl-3-alkylguaiazulene (16). Since the methyl group at the 4-position is 2-dimethylaminovinylated, these products show basic nature. In the case of diformyl products, methyne hydrogen of isopropyl group at the 7-position, which is not affected in usual substitutions, was substituted by formyl group. The Vilsmeier reaction of 4d gave 4 kinds of compounds similar to those products from 4a-4c, together with 4-(1-formylethyl) derivative (18d) and 2-formyl-4-(1-formyl-2-dimethylaminovinyl) derivative (19d). From the structures of these products, it was estimated that azulonium ions were formed by addition of the Vilsmeier reagent at the 1- or 3-position of 4 and consequently, the methyl group at 4-position and the isopropyl group at the 7-position were activated. On the basis of these facts, a mechanism of activation at side chains was discussed by examining the reaction pathes of 4. The reaction path of methine hydrogen in the isopropyl group at 7-position of (1) was shown as an example in the figure below. In this reaction, azulonium ion (1A) is formed by addition of N,N-dimethyliminium salt (abbreviated as A⁺, afterwards) formed from DMF-POCl₃ at the 1-position and consequently isopropyl group at the 7-position of (1) is activated. Then a methine hydrogen is evolved from dehydrogenation. A at the 1-position of (1B) is transformed to A⁺, which dislocate to α-carbon at the 7-position to form (2). From these reactions, it was shown that 4 can be activated by using a strong electrophilic reagent.



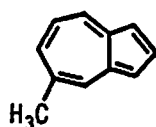
5. A simple approximation method of δ value of ¹³C-NMR for structure elucidation of azulenes¹⁴⁾

For structure elucidation of azulenes, ¹H-NMR spectrum is generally effective means. However, it was proved that there were some products that could not be analyzed by this mean but could only be analyzed by ¹³C-NMR spectrum. However, through ¹³C-NMR spectrum give a lot of information of saturated carbons, assignments of ring carbons in azulenes is very difficult by this means. And in order to easily use data from ¹³C-NMR spectrum for

structure elucidation of those reaction products, a simple method for calculation of an approximate chemical shift value (δ_A value) of ring carbon was devised, which facilitated assignment of the signals. The following is an example of the equation to calculate chemical shift in azulenes, in which a chemical shift value of substituted group (SCS value) for benzene is added to the standard chemical shift value of azulene derivatives of ^{13}C -NMR spectrum, some modifications have been made for azulenes, which has resulted in the least error between calculated and observed values for ring carbon, and also enough conformity in the order of the calculated values to those of observed ones for substituent carbons.

$$\delta_A = FVA_A + \sum_X k_A^d \cdot SCS^X_{(x,o,m,p)}$$

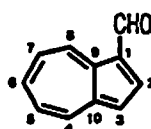
where FVA_A is chemical shift value in ring carbons of the standard compound, azulene (which varies from 118.8-140.2 ppm according to the position). k_A^d is the correlation coefficient for calculating SCS^X value of ring carbon at the A -position from SCS^X value of substituted group X in benzene derivatives. k_A^d was classified into Type I which has a predominant inductive effect, and Type M which has a predominant mesomerism effect. Parameter tables were prepared for each type. Means of SCS values for benzene published so far was adopted for SCS value. The reliability of assignment by the approximate method was confirmed with 33 of azulenes. On signals of 1 which is the fundamental compound of the reaction products mentioned so far, a thorough assignment was made through the approximation method and analysis of ^{13}C - ^1H coupling. Assignment of the signals in the reaction products did not involve any inconsistencies with the established structures.



5-Methylazulene

 δ_A

A	δ_A		D
	calcd.	obsvd.	
1	118.1	116.7	+1.4
2	136.9	137.1	-0.2
3	117.8	116.7	-1.1
4	137.1	138.1	-1.0
5	131.6	131.8	-0.2
6	137.6	138.3	-0.7
7	122.5	121.9	+0.6
8	133.8	134.8	-1.0
9	138.9	139.6	-0.7
10	140.1	139.9	+0.2



1-Formylazulene

 δ_A

A	δ_A		D
	calcd.	obsvd.	
1	126.6	125.8	+0.8
2	138.5	141.7	-3.2
3	118.7	119.1	-0.4
4	137.3	139.0	-1.7
5	128.5	128.2	-0.3
6	137.7	139.7	-2.0
7	128.5	129.4	-0.9
8	137.3	137.2	+0.1
9	141.4	140.2	-1.2
10	145.9	145.9	0.0

6. Conclusion

Azulene derivatives are now used in such limited fields as for medicines and optical-recording medium. The reason why they have only such limited uses in spite of the fact these compounds have long been known seem to be caused by the facts that they chiefly

have been studied from the standpoint of quantum chemistry and that reactions of azulenes have not been studied systematically owing to their similarity to benzoic aromatic compounds in the chemical properties. However, as industrial use and demand for azulene derivatives has been increased, detailed studies of azulene compounds have become needed. The author studied the reactions of guaiazulene (1), which is now manufactured in a large amount, not through its substitutional reaction which has already been studied so far but through their reactions of side chain of them. This study seems to have some contribution in the development of the method to synthesize some azulene derivatives with the unknown structures.

On the assumption that the side chains of guaiazulenes are activated when the contribution of azulonium ions becomes dominant in the resonance structures, the study was made and the following results were obtained:

1) It was found that 4-arylalkenes can be obtained as products from the reaction with a condensation reagent such as benzaldehyde when azulenes with an unsaturated bond such as acyl group at the 3-position are substituted by an electrophilic substituent group which can conjugate with azulene ring and subsequently the methyl group at the 4-position are activated. Among the reaction of 3-acylguaiazulenes (2) with formaldehyde, only the methyl group at the 4-position in 3-formylguaiazulene (2a) and 3-trifluoroacetylguaiazulene (2d), reacted to yield dioxane compounds (5). From these results, it was confirmed that there is a difference in the ability to activate the methyl group at the 4-position among the kinds of acyl groups. The reactions of 2d with formaldehyde gave cyclopenta[*c,d*] azulene derivatives, which suggests the possibility to synthesize polycyclic compounds from 2.

2) When 3-perfluoroacylguaiazulenes (2d)-(2e) were treated with ethanolic NaOH solution, followed by dehydration, cyclopenta[*c,d*] azulenes (9) were obtained in a good yield. On the basis of these reactions, a method to obtain acetylenes, which has promising uses as material for optical recording media, in a higher yield than the conventional method of synthesis by Hafner *et al.*, was developed. The method involves the reaction of 2a with active methyl ketone or other various ketones with active methylene group in ethanolic NaOH solution.

3) The side chain of 3-alkylguaiazulenes (4) was estimated not to be activated, which was supported by the experimental facts that it did not react at all with arylaldehydes. However, in a strong acid, a proton was added at the 1-position of 1,3-dimethylazulene and subsequently azulonium ion was formed and it dissolved. Since the same reaction is estimated to occur with 4, it was expected that if 4 is allowed to react with some active reagent behaving as cation such as proton, the 1- or 3-position in 4 will undergo addition and the activation of side chain will occur as the result of formation of azulonium ion.

4 was made to react with the Vilsmeier reagent composed of *N,N*-dimethylformamide and phosphorous oxychloride, which resulted in various products from the reaction of the methyl group at the 4-position as well as the isopropyl group at the 7-position of 4. From the structures of these products, it was proved that the addition of the Vilsmeier reagent

at the 1- or 3-position of 4 occurred to form azulonium ion, which resulted in activation of the methyl group at the 4-position or the isopropyl group at the 7-position to yield various compounds. Therefore, the following two methods proved to have become available to activate side chain of guaiazulenes: (1) To substitute an electrophilic group such as acyl group which can conjugate with azulene ring. (2) To make react with a strong active reagent which behaves as cation when the 3-position is substituted by a group with a relatively weak induced effect such as alkyl group.

4) In the process of study on synthesis of these azulene derivatives, ^{13}C -NMR spectrum was used as a means for structural analysis. Though it proved to be very difficult for general assignment of the signals from azulene ring carbons, the author developed a simple method to calculate chemical shift in azulene ring carbon and to easily assign its structure. The method was adopted for structural analysis of the azulene derivatives synthesized here. The reactions of azulenes has chiefly been studied on their substitution ones so far.

The author paid attention to the side chain of azulenes, and studied methods to activate their side chains. As a result, the author found some useful new reactions. Especially, a new method to synthesize aceheptylenes developed here is considered to be an attractive one from the industrial standpoint in that the reaction involved is easily to react compared with the method by Hafner *et al.* and reagents used are relatively cheap. Among the Vilsmeier reaction products of 4, some are reported to have possibilities as inhibitors on cancer. If these reactions of side chains are applied to alkylazulenes besides guaiazulenes, a number of useful azulene derivatives are expected to be synthesized in the future.

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