CCA - 75 547.913.5:542.91

Synthesis of Azulenoids from Troponoids

Tetsuo Nozoe

Chemical Institute, Tohoku University, Sendai, Japan

Received July 18, 1957

I. INTRODUCTION

Azulenes have drawn the interest of many a chemist in the past because of its deep color but their structure remained concealed for a long time. Professor Ruzicka, the originator of fundamental studies on polyterpenoid and elaborator of this system, and his school have long carried out studies on sesquiterpenes which are closely related to azulene and they pointed out the fact that the structure of azulenes is a special bicyclic system different from the benzenoid ring.[1]

With these studies as the basis, Pfau and Plattner established the structure of azulenes as composed of unsaturated, seven- and five-membered rings and the synthesis of their parental compound, azulene, was completed in 1937.[2] This was followed by the syntheses of various azulene derivatives by numerous chemists. The known process of azulene synthesis generally calls for the dehydrogenation of bicyclic hydrocarbons at a high temperature and cyclodecane or even normal butane have been employed.[3] These processes for the synthesis of azulenes invariably required dehydrogenation reaction at around 300° in the last stage and, although many improvements have been effected, the yield has been generally poor.

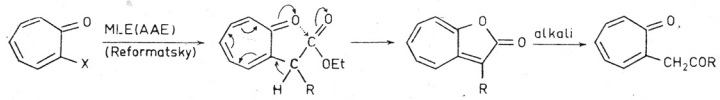
Recently, Ziegler and others developed a novel synthetic process starting with pyridine and cyclopentadiene, and this has made it possible to synthesize azulenes possessing alkyl, phenyl, dimethylamino, and other substituent groups. Ziegler has also found a process of introducing alkyl and phenyl groups into 4- and 8-positions of the azulene skeleton.[4] However, even this new process of azulene synthesis by Ziegler requires a high-temperature treatment at above 200°, that it would difficult to prepare azulenes possessing heat-labile groups, such as mercapto, amino, hydrazino groups, and amino acid side chain, by this method.

On the other hand, studies on the aromaticity of troponoid compounds have made a large progress and in connection with these, the substitution reaction of azulenes, also possessing an unsaturated, seven-membered ring, has been taken up. Consequently, it became known that a halogen, nitro, acetyl, and azo groups could be introduced into 1- and 3-positions of azulene by the application of a cationoid reagent,[3] but since the kind and position of the group introduced on the azulene ring by this cationoid substitution are limited, the number of azulene derivatives that can be obtained through this reaction remained in a certain number.

For the past few years, studies on troponoid have been carried out in the writer's laboratory.[5] As a part of such studies, reaction of anionoid reagents on troponoid was examined from various angles and it was discovered that the reaction of 2-halotropone and tropolone methyl ether with guanidine, thiourea, malonic ester, and cyanoacetic ester resulted in a cyclization to a five-membered ring, forming numerous compounds possessing a new azulene-type ring system. This synthetic procedure will be explained in some detail in the following sections.

II. 1-OXAAZULAN-2-ONE

Application of sodium salt of malonic, acetoacetic, or acetonedicarboxylic ester to 2-chlorotropone (I) affords 3-ethoxycarbonyl- (II) and 3-acetyl-1-oxa-azulan-2-one (III),[6] and similar compounds.[7] On heating (II) and (III) in 75% sulfuric acid, they form parental 1-oxaazulan-2-one (IV). Application of bromo-acetic ester to (I) and 2-methoxytropone (V), under conditions for the Reformatsky reaction, also affords (IV)[8], while mild treatment of (II) and (III) with alkali results in the opening of the lactone ring and 2-troponylacetic acid (VI) and 2-troponylacetone (VII) are formed.



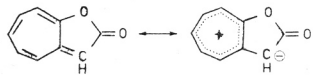
I. X= Cl
V. X= OMe

II. R = COOEt
III. R = COMe
IV. R = H
IX. R = Br
X. R = NO_2
XI. R = NH_2

VI. R = OH
VII. R= Me

(IV) also takes an ionic structure (VIII) similar to azulene itself and its 3-position has a high electron density that substitution with electrophilic reagents occur in this position.

For example, acetylation of (IV) by the Friedel-Crafts reaction results in the formation of a 3-acetyl derivative (III) and bromination and nitration give 3-bromo (IX) and 3-nitro derivative (X)[8].

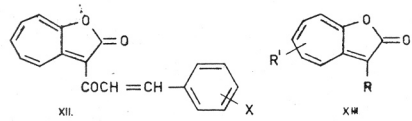


IV. VIII.

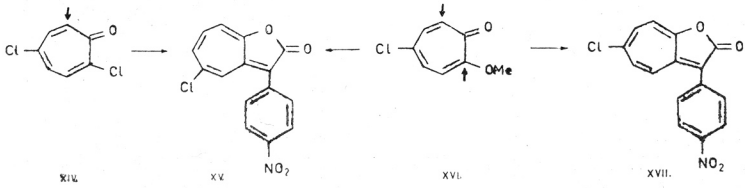
The dipole moment of (IV) is 5.7 D and such a large value indicates the great contribution of ionic structure (VIII)[9]. This fact is also endorsed from X-ray diffraction data.[10]

The 3-nitro compound (X) is also obtained by the condensation of (I) and nitroacetic ester and (X) is reduced to the 3-amino compound (XI). Similar to aromatic amines, (XI) forms 3-halogen compounds by the Sandmeyer reaction, while the 3-acetyl compound (III) undergoes condensation with benzaldehyde derivatives to form various cinnamoyl derivatives (XII).[8]

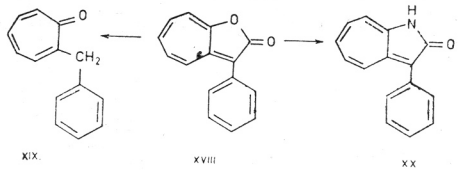
Many kinds of 1-oxaazulan-2-one derivatives (XIII) are formed on the application of malonic, acetoacetic, nitroacetic, or phenylacetic ester to alkyl or other substituted 2-chlorotropones and 2-methoxytropones.



In these condensation reactions, abnormal substitution often occurs. For example, condensation of 2,5-dichlorotropone (XIV) and *p*-nitrophenylacetic ester in benzene solution results in the sole formation of a 5-chloro derivative (XV) by abnormal substitution, while 2-methoxy-5-chlorotropone (XVI) affords 6-chloro derivative (XVII) under the same conditions. On the other hand, reaction of (XVI) in benzene-ether (mixed solvent) affords a mixture of (XV) and (XVII).[8]

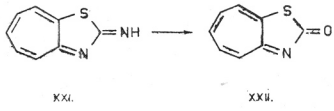


Treatment of 3-phenyl-1-oxaazulan-2-one (XVIII) with alkali gives 2-benzyltropone (XIX), while its treatment with alcoholic ammonia affords 3-phenyl-1-azaazulan-2-one (XX).[8]



III. 1-THIA-3-AZAAZULAN-2-ONE

Reaction of 2-chlorotropone (I) and thiourea results in the formation of 1-thia-3-azaazulan-2-onimine (XXI) and the use of 2-methoxytropone (V) in place of (I) in this reaction merely affords a molecular compound. In the presence of alkali, however, this reaction gives a 1,3-diazaazulene derivative, as will be described later. When (XXI) is heated with hydrochloric acid, it forms 1-thia-3-azaazulan-2-one (XXII).

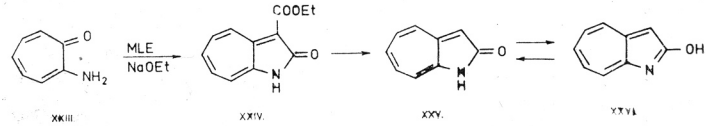


Alkyl derivatives of (XXI) and (XXII) are obtained from the alkyl derivatives of (I) by a similar reaction. (XXI), (XXII), and their derivatives easily form molecular compounds like picrate and styphnate, and show some interesting biochemical[11] and biological[12] activities.

IV. 1-AZAAZULENE

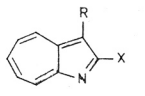
i) *From 2-Aminotropone*

Reaction of 2-aminotropone (XXIII) and malonic ester, in the presence of an alkoxide, affords 3-ethoxycarbonyl-1-azaazulan-2-one (XXIV), whose hydrolysis and decarboxylation with hydrobromic acid give 1-azaazulan-2-one (XXV). The ultraviolet spectrum of (XXV) is more similar to the aforementioned 1-oxaazulan-2-one (IV) than to that of 2-chloro-1-azaazulene (XXVIII) to be described later that it would appear that (XXV) is present in its keto form (XXV) rather than as 2-hydroxy-1-azaazulene (XXVI).



XXIII XXIV XXV XXVI

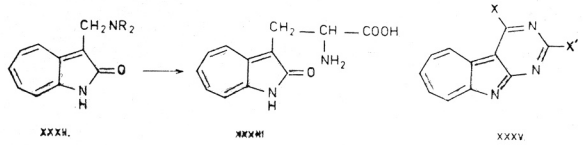
On the application of phosphoryl chloride, (XXIV) and (XXV) respectively form 3-ethoxycarbonyl-2-chloro-1-azaazulene (XXVII) and 2-chloro-1-azaazulene (XXVIII). The chlorine atom in (XXVII) and (XXVIII) are highly reactive and easily undergo exchange reactions with anionoid reagents, such as bromide, alkoxides, amines, hydrazines, mercaptides, cyanides, malonic ester, and cyanoacetic ester, to form derivatives possessing various substituents in the 2-position. Decomposition of the 2-hydrazino compound (XXIX) with copper sulfate in acetic acid affords the parental compound, 1-azaazulene (XXX), a very labile, red oil that turns into purplish black solid when left in the air.



XXVII. R = COOEt, X = Cl
XXVIII. R = H, X = Cl
XXIX. R = H, X = $NHNH_2$
XXX. R = X = H
XXXI. R = H, X = $N(Me)_2$
XXXIV. R = COOEt, X = NH_2

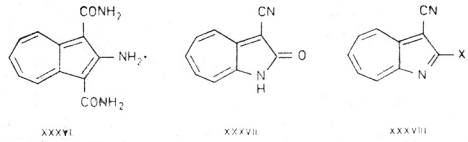
(XXX) and its derivatives are generally susceptible to electrophilic substitution in the 3-position, while (XXV) and 2-dimethylamino derivative (XXXI) undergo very facile azo coupling and nitrosation in the 3-position to form the corresponding derivatives.[13]

1-Azaazulene derivatives form various Mannich bases by the Mannich reaction and give 3-formyl derivatives by reaction with dimethylformamide and phosphorylchloride. This process of azaazulene synthesis is also utilized in the case of 2-aminotropone derivatives possessing alkyl, aryl, and halogen substituents, forming corresponding 1-azaazulenes.[14] For example, the Mannich base (XXXII) of (XXV) gives a seven-membered ring compound (XXXIII) allied to tryptophan and a tricyclic compound like (XXXV) is obtained from 2-amino-3-ethoxycarbonyl-1-azaazulene (XXXIV).[8]



ii) *Action of Cyanoacetamide on Troponoids*

Application of cyanoacetamide to 2-chlorotropone (I) or 2-methoxytropone (V) at room temperature, in the presence of an alkoxide, results in the formation of 3-cyano-1-azaazulan-2-one (XXXVII) as the main product, besides a small amount of an azulene derivative (XXXVI). Treatment of (XXXVII) with phosphoryl chloride changes it to the 2-chloro derivative (XXXVIII: X=Cl), which can be converted to various derivatives.



Application of this process to the tropone derivatives possessing alkyl and other substituents gives 1-azaazulene derivatives with various substituents on the seven-membered ring. It should be remembered, however, that the cyclization into five-membered ring takes place in a different position according to whether the starting compound is a 2-chloro or 2-methoxy derivative and by the steric effect of the substituent on the seven-membered ring.

For example, application of cyanoacetamide to the two methyl ethers (XXXIX and XL) obtained from 4-methyltropolone results in the formation of (XLI) and (XLII), whose treatment with phosphoryl chloride affords 2-chloro-3-cyano compounds (XLIII and XLIV). On the other hand, condensation of malonic ester with 2-amino-4-methyltropone (XLV) obtained from one (XL) of the foregoing methyl ethers gives (XLVI), and the 2-chloro-3-cyano derivative obtained from it through the acid amide (XLVII) agrees with (XLIII). The 2-chloro-3-cyano derivative, obtained from the 2-aminotropone derivative (XLVIII) by the same reaction agrees with (XLIV) (cf. Chart 1). It is known from the foregoing facts that in reaction with cyanoacetamide, the carbon-carbon linkage in the newly formed five-membered ring is produced between the carbon with the methoxyl in the tropone ring and the carbn atom in active methylene group of the acetamide, while the carbon-nitrogen bond is produced between the carbonyl in the tropone ring and nitrogen in the amino group of the acetamide.

On examining the structure of the products formed in these reactions by the manner described above, it was found that abnormal substitution reaction invariably takes place when 2-chlorotropone derivative is used in place of 2-methoxytropone derivatives. For example, (LIII) is obtained from (LI) and (LIV) from (LII). In the case of 3-methyl-2-methoxytropone (LV), however, abnormal reaction occurred to give (LVI), in spite of the fact that it is a methoxytropone derivative. Chlorotropone derivatives that cannot

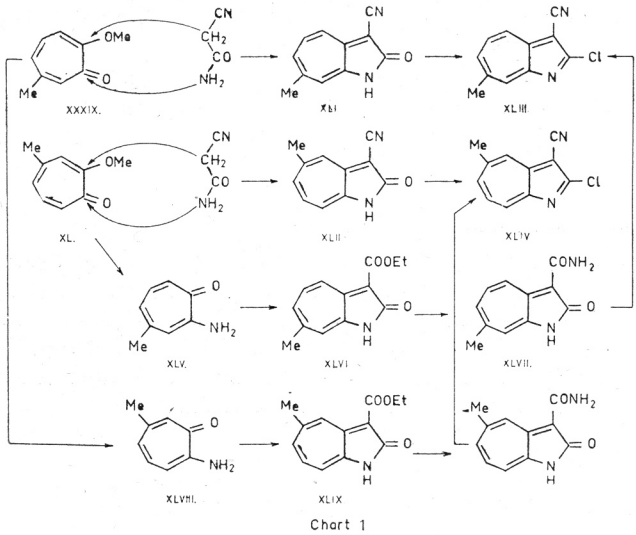
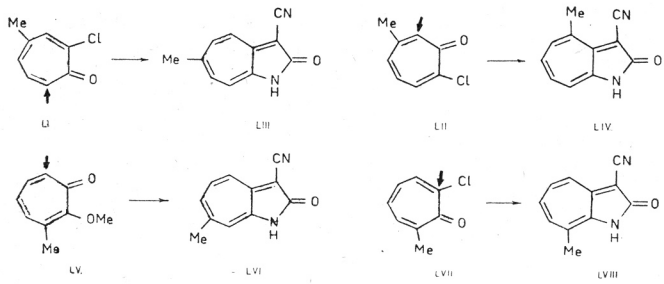


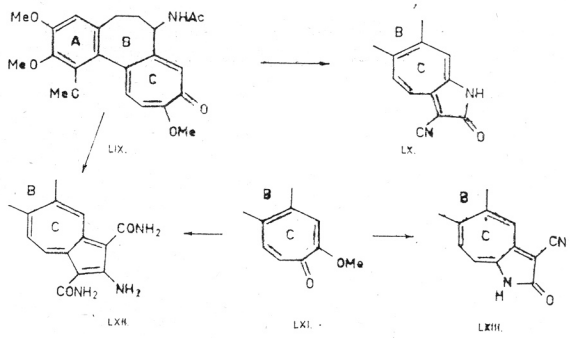
Chart 1

undergo abnormal substitution, such as (LVII), undergoes normal substitution and forms (LVIII).[14] The position of substituents in these products can be surmised to a certain extent by the C-H out-of-plane absorption in the region of 700—900 cm^{-1}.[8]



Cook and others obtained a condensation product corresponding to $C_{24}H_{24}O_5N_3Cl$ by the application of cyanoacetamide to colchicine (LIX), in the presence of an alkoxide, but the structure of this condensation product was not revealed at that time because the tropolonic structure of colchicine was not known then[15]. However, the structure (LX) can now be assigned to this condensate from the results of a series of experiments described above.

It has been revealed by recent experiments in the writer's laboratory that application of cyanoacetamide to colchicine (LIX) and isocolchicine (LXI) afforded an azaazulene derivative (LX) and an azulene derivative (LXII) from (LIX), and chiefly azulene derivative (LXII) and a small amount of azaazulene derivative (LXIII) from (LXI).[8]



iii) *Application of Indole Synthesis*

Application of Fischer's indole synthesis to the condensation product (LXIV) of 2-hydrazinotropone and phenylacetaldehyde results in the formation of 3-phenylpyrrolotropone (LXV), which gives the 8-chloro derivative (LXVI: X=Cl) by the action of phosphoryl chloride. Decomposition of the hydrazino compound (LXVI: X=NHNH$_2$), obtained from this chloro derivative, with copper sulfate gives 3-phenyl-1-azaazulene (LXVI: X=H).[16] On the other hand, application of thionyl chloride to (LXV) results in the chlorination of the 2-position as well and 2,8-dichloro compound (LXVII: X=Cl) is obtained.[8]

The 8-chloro (LXVI: X=Cl) and 2,8-dichloro compounds (LXVII: X=Cl) can be derived to various substitution products by reaction with anionoid reagents,[8] as indicated in the Chart 2.

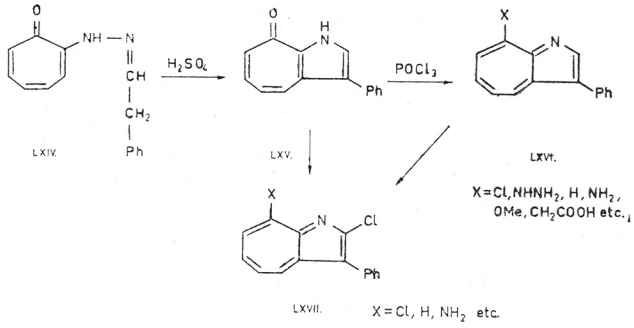
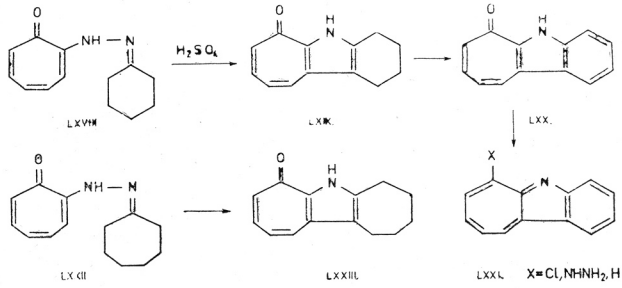


Chart 2.

iv) *Application of Carbazole Synthesis*

When the condensation product (LXVIII) of 2-hydrazinotropone and cyclohexanone is warmed with concentrated sulfuric acid, the compound undergoes cyclization into a pyrrole ring, as in the case of Borsch's carbazole synthesis, and pyrrolotropone derivative (LXIX) is formed. The dehydrogenation of (LXIX) with chloranil affords indolotropone (LXX) and this compound can be converted to 2,3-benz-1-azaazulene (LXXI: X=H) via the chloro compound (LXXI: X=Cl) and hydrazino compound (LXXI: X=NHNH$_2$).

In a similar manner, the condensation product (LXXII) of 2-hydrazinotropone and cycloheptanone affords 2,3-pentamethylene-1-azaazulene derivative (LXXIII).[8]

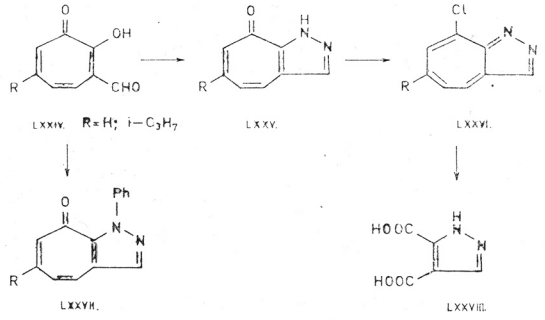


2,3-benz-1-azaazulene has already been obtained by Anderson and Treibs using another method.[17]

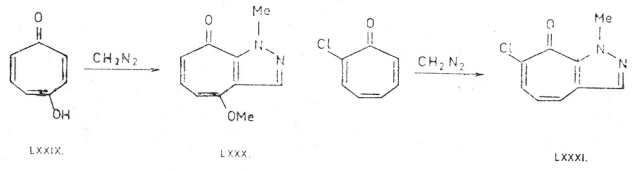
V. 1,2-DIAZAAZULENE

Application of hydrazine to 3-formyltropolone (LXXIV: R=H) or its *iso*-propyl derivative (LXXIV: R=*iso*-C_3H_7) affords pyrazolotropones (LXXV) which is converted to the chloro derivative (LXXVI) of 1,2-diazaazulene on the application of phosphoryl chloride. Oxidation of (LXXVI) gives pyrazole-3,4-dicarboxylic acid (LXXVIII) so that the structure of (LXXVI) is established.

Application of phenylhydrazine to (LXXIV) gives the *N*-phenylpyrazolo derivatives (LXXVII).[18]



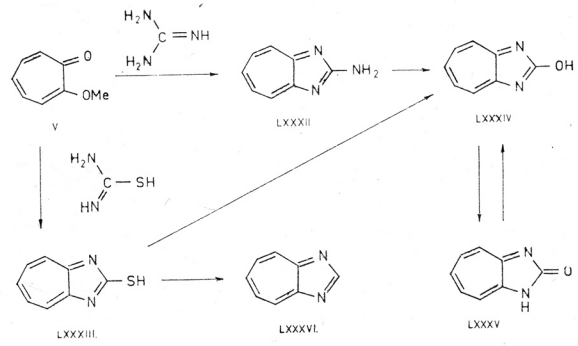
Application of diazomethane to 4-hydroxytropone (LXXIX) and 2-halotropone also affords the corresponding pyrazolotropone derivatives (LXXX and LXXXI).[8]



VI. 1,3-DIAZAAZULENE

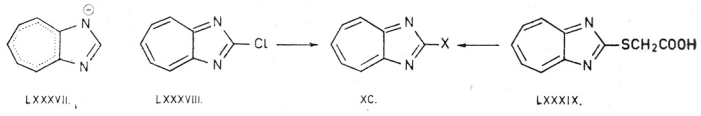
Reaction of 2-methoxytropone (V) with guanidine or thiourea, in the presence of alkali or alkoxide, affords 2-amino- (LXXXII) or 2-mercapto-1,3-diazaazulene (LXXXIII) in a good yield. In this reaction, the use of urea results in the formation of only a molecular compound and not the condensation product. Hydrolysis of the 2-amino compound (LXXXII) with concentrated hydrochloric acid or desulfurization of the 2-mercapto compound (LXXXIII) with mercury oxide results in the formation of 2-hydroxy-1,3-diazaazulene (LXXXIV).[19] The 2-hydroxy compound (LXXXIV) exists as keto-enol tautomers, but from its reactivity and ultraviolet spectrum, it is known to be present mostly in its keto form (LXXXV).[19]

Oxidation of 2-mercapto compound (LXXXIII) with nitric acid or hydrogen peroxide gives the parental compound 1,3-diazaazulene (LXXXVI).[19]



Since 1,3-diazaazulene (LXXXVI) possesses a large dipole moment (4.03 D),[9] it is known that there is a great contribution of ionic structure like (LXXXVII). In this case, the 1- and 3-position with high electron density are occupied by nitrogen atoms that cationoid substitution reaction does not take place.

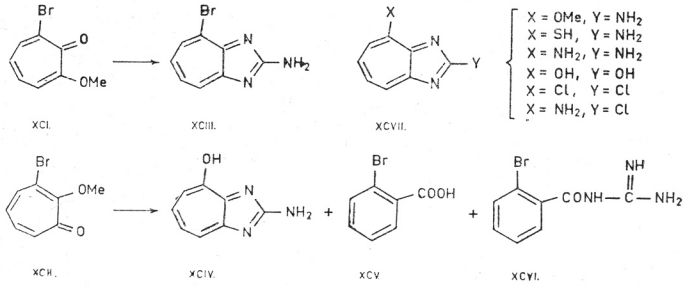
2-Chloro-1,3-diazaazulene (LXXXVIII) is obtained on the application of phosphoryl chloride to 2-hydroxy compound (LXXXIV), and application of monochloroacetic acid to the mercapto compound (LXXXIII) affords (LXXXIX). (LXXXVIII) and (LXXXIX) are easily derived to various 2-subtituted compound (XC) by the action of ammonia, amines, or hydrazine.[8]



By the condensation of the alkyl,[20] aryl,[20] or styryl[20] derivative of tropolone with guanidine or thiourea, corresponding derivatives of 1,3-diazaazulene are obtained.

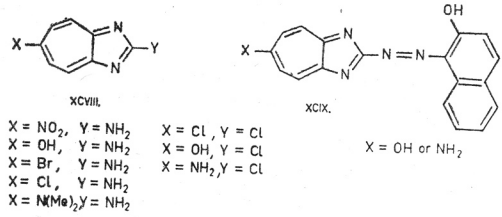
Condensation of the two methyl ethers (XCI and XCII) of 3-bromotropolone with guanidine affords 1,3-diazaazulene derivative (XCIV) from (XCI), and a small amount of 1,3-diazaazulene derivative (XCIV) from (XCII) but majority of (XCII) undergoes rearrangement to give (XCV) and (XCVI).

The bromine atom in 2-amino-4-bromo-1,3-diazaazulene (XCIII) is susceptible to nucleophilic substitution and the amino group also changes to the hydroxyl group by the action of acid or alkali. In such a manner, 2,4-dihydroxy derivative (XCVII: X=Y=OH) is obtained. This dihydroxy compound is converted to the dichloro derivative (XCVII: X=Y=Cl) by the action of phosphoryl chloride and then derived to various substitution products (XCVII).

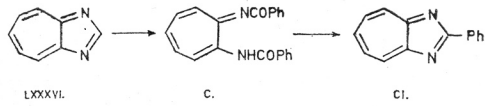


Similarly, substitution product like (XCVIII) is obtained by the condensation of 5-substituted tropolone methyl ether and guanidine, and the 2- and 6-positions in (XCVIII) also submit to anionoid substitution, as in (XCVII). It is interesting to note that in these reactions, the substituent in 4- or 6-position is more easily attacked than that in 2-position.

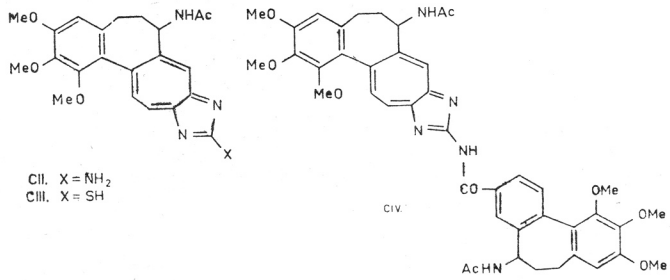
The amino group in 2-amino-1,3-diazaazulene (LXXXII) is not diazotized by the action of nitrous acid but is diazotized if there is a hydroxyl or amino group at 6-position, undergoing coupling with β-napthol to form a dye like (XCIX).



Attempted benzoylation of the parental compound, 1,3-diazaazulene (LXXXVI), results in the opening of the five-membered ring once to form (C), which again undergoes cyclization easily to give 2-phenyl-1,3-diazaazulene (CI).

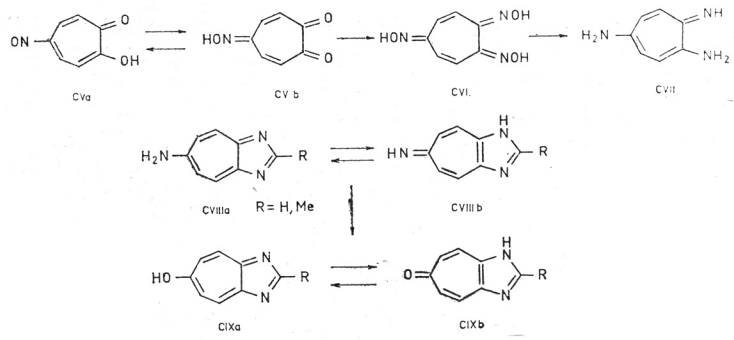


Application of guanidine or thiourea to colchicine, in the presence of alkali, similarly affords corresponding condensation product (CII or CIII).[21] The condensation of colchicine and guanidine was also carried out by Fourneau and he obtained (CIV) besides (CII).[22]



Tropoquinone trioxime (CVI) formed by the reaction of nitrosotropolone (CV) and hydroxylamine is reduced to 2,5-diaminotroponimine (CVII),[23] whose reaction with formic or acetic acid affords 6-amino-1,3-diazaazulene derivative (CVIII).

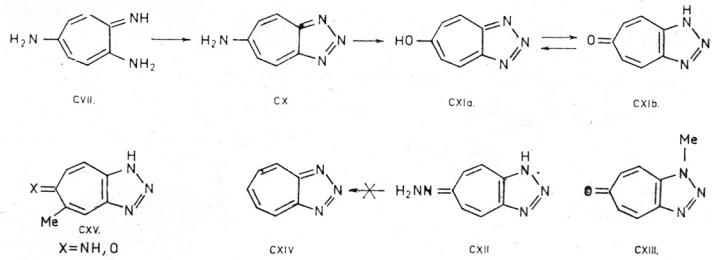
The amino group in the 6-position of (CVIII) does not show properties of a primary amine and its hydrolysis gives the 6-hydroxy derivative (CIX), whose ultraviolet spectrum and other properties suggest that it takes the keto form (CIXb).[24]



VII. 1,2,3-TRIAZAAZULENE

The afore-mentioned 2,5-diaminotroponimine (CVII) reacts with nitrous acid to form 6-amino-1,2,3-triazaazulene (CX) and this amino group also does not behave like a primary amino group. Alkaline hydrolysis of (CX) affords the 6-hydroxy compound (CXI) which reacts with ketonic reagents to form the hydrazone (CXII), oxime, and 2,4-dinitrophenylhydrazone. Methylation of (CXI) with diazomethane or dimethyl sulfate and alkali gives the *N*-methyl compound (CXIII). These facts suggest that (CXI) exists in its keto form (as triazolotropone (CXIb)). (CXII) does not form the parental 1,2,3-triazaazulene (CXIV) on treatment with copper sulfate.[25]

4-Methyl-5-nitrosotropolone can be derived to the corresponding methyl homolog (CXV) of 1,2,3-triazaazulene.

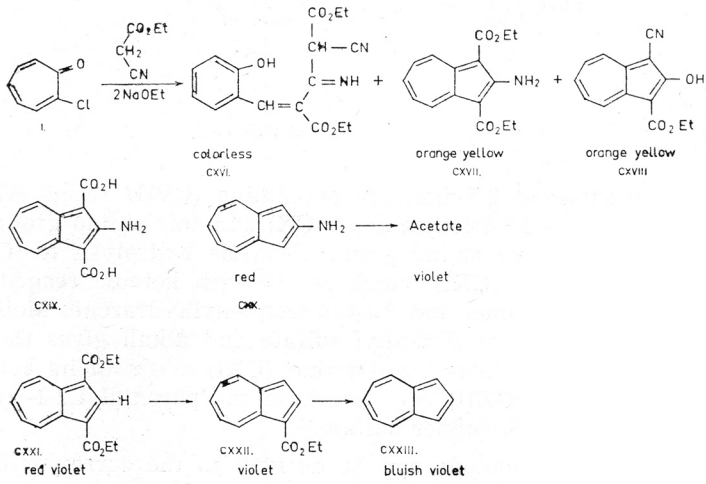


VIII. AZULENE DERIVATIVES

i) *A New Synthetic Method for Azulene Derivatives*

During 1953, an interesting phenomenon was found in the writer's laboratory. A mixture of 2-chlorotropone and two or three equivalents of cyanoacetic ester in ethanolic solution, in the presence of two equivalents of alkoxide, was allowed stand at a room temperature and, after a few hours, sparingly soluble sodium salt precipitated out. From its mother liquor, colorless crystals (CXVI) of m. p. 136° and orange yellow crystals (CXVII) of m. p. 93° were obtained. From the sodium salt, a yellow, acid substance (CXVIII) of m. p. 189° was obtained.

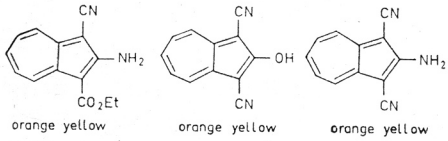
The main product (CXVII) was obtained in around 70% yield and, from its analytical values ($C_{16}H_{17}O_4N$) and infrared spectra, it was found to have two ethoxycarbonyl groups and one amino group. Its hydrolysis followed by decarboxylation afforded a red-colored, monoamino compound (CXX) ($C_{10}H_9N$), whose acetylation changed it to violet crystals of m. p. 168°. From the marked change of color by the slight difference in structure, it was assumed that the substance (CXVII) obtained here might possess an azulenic skeleton. Therefore, (CXVII) was submitted to deamination by the Griess reaction and reddish violet crystals (CXXI) of m. p. 121° were obtained. Its hydrolysis followed by heating easily gave violet 1-ethoxycarbonylazulene (CXXII) and bluish violet



azulene (CXXIII).[26] At that time, it was not even considered possible that the product (CXVII), so easily obtained in one step, would be an azulene derivative, more so, because of its yellow color.

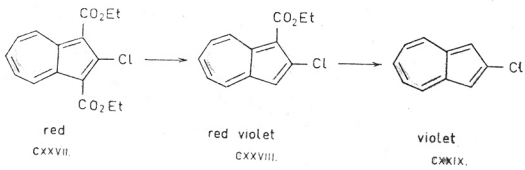
The other compound (CXVIII) was also found to be an azulene derivative possessing a cyano, hydroxyl, and ethoxycarbonyl groups.

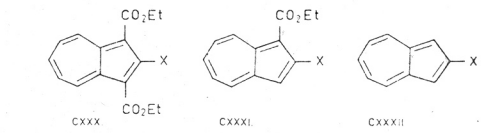
Similar application of cyanoacetic ester to tropolone methyl ether affords an acid substance (CXXV), as the chief product, besides orange yellow crystals (CXXIV) of m. p. 137° and (CXVII).



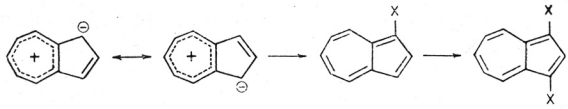
The reaction of 2-chlorotropone with malononitrile results in the formation of orange-yellow, dicyano-aminoazulene (CXXVI). It has already been shown that the application of cyanoacetamide to 2-chlorotropone or tropolone methyl ether affords an azulene derivative (XXXVI) as one of the products[14] [cf. Section IV (ii)].

Application of nitrous acid to 2-aminoazulene (CXX) results in the change of colour from green to brown and pure product cannot be isolated but the same application to the hydrochloride of (CXVII) results in facile substitution of the 2-amino group with chlorine to form a red compound (CXXVII). Its hydrolysis followed by decarboxylation affords violet 2-chloroazulene (CXXIX),[27] but under certain conditions, 1-ethoxycarbonyl-2-chloroazulene (CXXVIII) is formed.[8] The chlorine atom in these compounds underoges substitution not only with iodine atom by the application of hydriodic acid, but also with alkoxyl, mercapto, amino, and hydrazino groups, as well as numerous kinds of anionoid reagents such as malonic, cyanoacetic, and acetoacetic esters, to form many new 2-substituted azulene derivatives (CXXX, CXXXI and CXXXII).[8]





Azulene (CXXIII) is stabilized by the contribution of ionic structures, as in the case of tropolone, and its 1- and 3-positions can be introduced with chloro, bromo, acetyl, nitro, azo, and sulfonic acid groups by cationoid substitution reactions. Condensation with benzaldehyde also occurs in these positions.[28, 29]

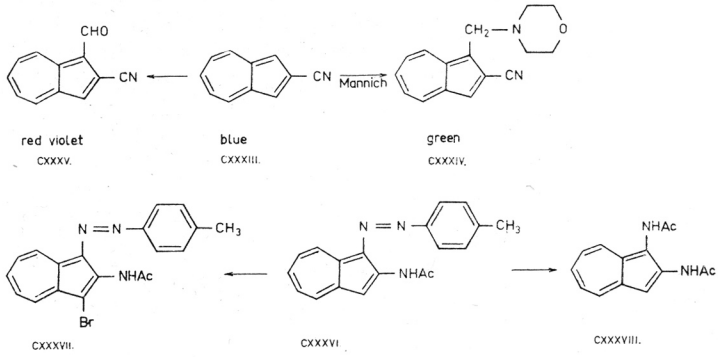


X= Cl, Br, NO_2, COMe, N= N—Ph

It has also been found that azulene easily undergoes Mannich reaction, and formylation with dimethylformamide giving compounds such as (CXXXIV) and (CXXXV),[8] and new derivatives of azulene are being prepared one after the other from these compounds.

Substituents cannot be introduced by the cationoid reaction in general into the seven-membered ring of azulene because of its low electron density, but azulenes with substituents in the seven-membered ring can be obtained easily by the use of a tropolone already possessing a substituent, such as alkyl, aryl, halogen, cyano, alkoxycarbonyl, etc., in its ring.

This new method of preparing azulene is advantageous in that the azulene derivatives are obtained in one step, in a good yield, and at low temperatures, making it possible to prepare compounds having heat-labile functional groups. Therefore, substituents are not restricted to amino and hydroxyl groups which can be changed later but functional groups that cannot be introduced later may be had in azulenes prepared by this method.[8]

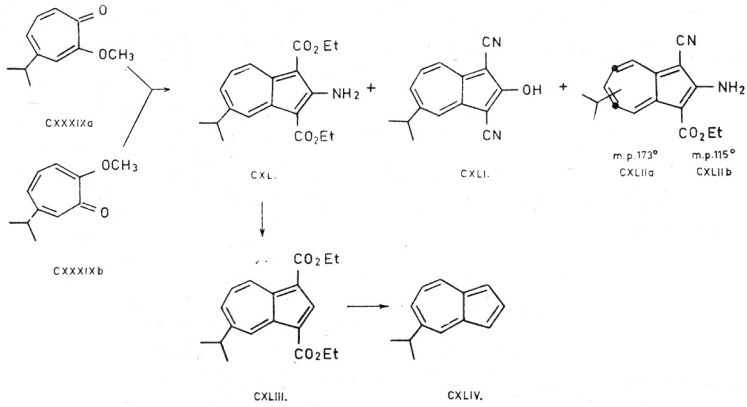


ii) *Application of the New Synthesis to Various Tropolone Derivatives*

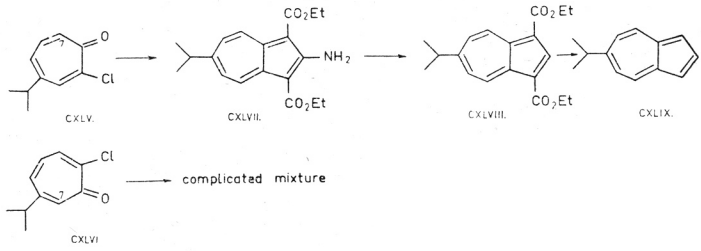
As described in the foregoing section, the new synthetic procedure for azulenes can be applied to various tropolone derivatives and the structure and kind of products obtained from this reaction differ according to a variety of conditions, such as the structure of the troponoid used, kind and amount of the condensation agents used, and the solvent.

Reaction of hinokitiol methyl ethers (CXXXIXa) (CXXXIXb) with cyanoacetic ester, in the presence of an alkoxide, affords (CXL), (CXLI), and

(CXLIIa and b),[27] and the ratio of these products differs markedly according to the amount of the alkoxide used.[8] As was shown earlier with the compound (CXVII), deamination of (CXL) followed by hydrolysis, and decarboxylation affords 5-*iso*-propylazulene (CXLIV), as anticipated.



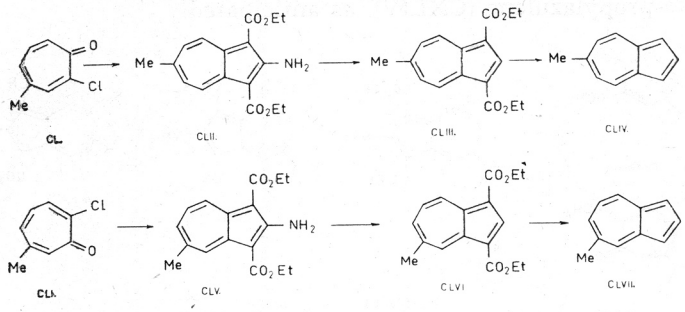
The two methyl ethers (CXXXIXa and CXXXIXb) can be derived to two kinds of chloro-*iso*-propyltropone (CXLV and CXLVI), separately through their respective hydrazino compounds. Application of cyanoacetic ester to one (CXLV) of them affords a condensation product (CXLVII), in a good yield of over 70%, and this product can be converted to 6-*iso*-propylazulene (CXLIX).[27]



It is clear that an abnormal substitution reaction occurs in this case, two moles of cyanoacetic ester having formed a five-membered ring with the carbonyl carbon and the carbon at 7-position. This tendency is observed often in reactions of troponoids and this kind of abnormal (or cine) reaction seems to occur preferentially in chlorotropones.

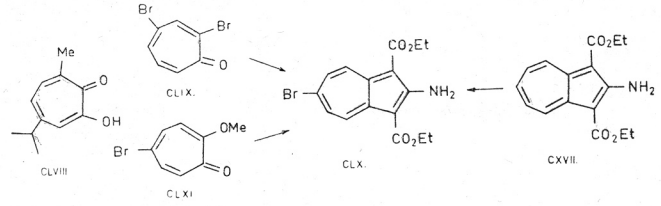
On the contrary, the other isomer (CXLVI) also reacts with cyanoacetic ester but does not give products corresponding to (CXL) or (CXLVII), the product obtained being a complicated mixture of five or six kinds of substances. This is probably due to the steric interference of the *iso*-propyl group, by which the adjacent 7-position is not easily attacked by the anionoid reagents, and results in some other reactions. The fact that this assumption is true is proved in the case of a chlorotropone derivative (CLI) with a methyl group instead of *iso*-propyl group in the 6-position, from which 5-methyl-

azulene derivative (CLV) is obtained in around 5% yield by normal substitution, and (CLV) is converted to 5-methylazulene (CLVII).[8]



Reaction of the methyl ether of 7-methylhinokitiol (CLVIII) with cyanoacetic acid, in an attempt to prepare guaiazulene, forms the objective azulenoid compound in a very poor yield, and tropone derivatives without formation of the five-membered ring are chiefly obtained.[8]

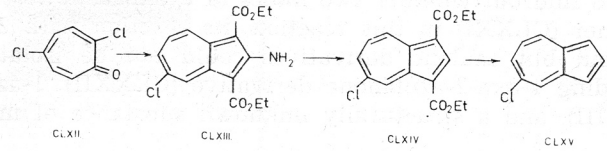
2,4-Dibromotropone (CLIX) also undergoes abnormal (cine) substitution reaction to form 6-bromoazulene derivative (CLX). It is interesting to note that this compound (CLX) is also obtained by the condensation of 5-bromo-2-methoxytropone (CLXI) and cyanoacetic ester or by the bromination of the aforementioned (CXVII) in chloroform. Such bromination can be effected in 6-position even if the amino group in 2-position of (CXVII) is derived to methylamino group, but the bromination is no longer possible when it is derived to dimethylamino group.[8]



Condensation of 2,5-dichlorotropone (CLXII) with cyanoacetic acid affords 5-chloroazulene derivative (CLXIII), which can be derived to 5-chloroazulene (CLXV) itself. It has been reported[30] that (CLXV) is obtained by the Reimer-Tiemann reaction of indenylsodium.

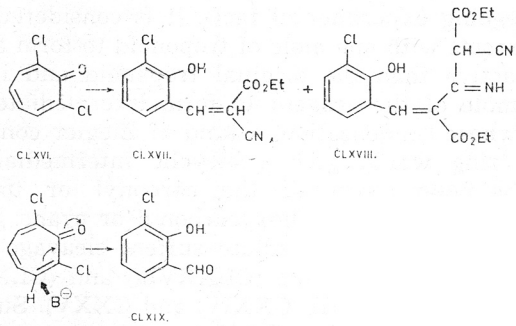
The number of new azulene derivatives that can be obtained has increased by such means and it has become possible to presume the position of their side chain by examining the C-H out-of-plane absorption at 700—890 cm^{-1} in their infrared spectra[8], as the case of 1-azaazulene derivatives.

In the case of 2,7-dichlorotropone (CLXVI), application of cyanoacetic ester does not give any azulene derivative and the products are two kinds of compounds (CLXVII and CLXVIII) formed by rearrangement.



CLXII CLXIII CLXIV CLXV

The colorless by-product (CXVI), obtained during the reaction of 2-chlorotropone and cyanoacetic ester described earlier, corresponds to this compound (CLXVIII) without chlorine atom,[8,27] and this kind of rearrangement is often witnessed in the reaction of halotropones. For example, treatment of (CLXVI) with ethanolic alkali or ammonia is known to give chlorosalicylaldehyde (CLXIX)[31] and in this case, the anionoid reagent is thought to have attacked the C-3 position in the tropone ring.[32] In the attempted synthesis of azulene derivative mentioned above, it is assumed that the reaction occurred either by the direct attack of the reagent at 3-position or by the secondary reaction of the reagent with the salicylaldehyde derivative first formed.



CLXVI. CLXVII. CLXVIII.

CLXIX.

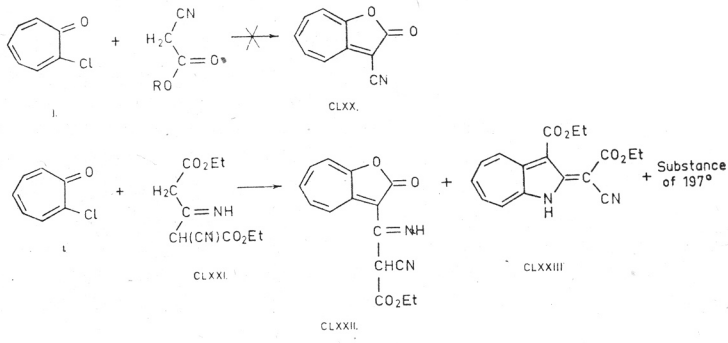
iii) *Considerations on the Reaction Mechanism*

Studies have been made in the past for the reaction mechanism involved in the new method for synthesis of azulenes mentioned above but no conclusive result has yet been obtained due to the complexity of reaction products and formation of the final product in one step, without the isolation of any intermediate compounds.

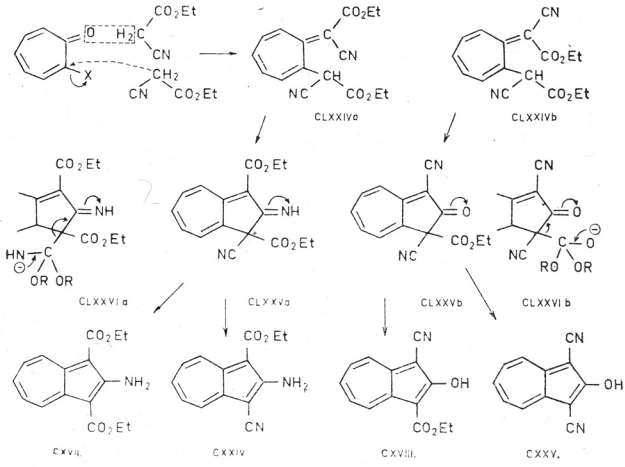
This reaction was first carried out under the assumption that the reaction of 2-halotropone and cyanoacetic ester would afford 3-cyano-1-oxa-2-azulanone (CLXX), as in the formation of 1-oxa-2-azulanone derivatives (II and III)[6] by the reaction of 2-halotropone and malonic or acetoacetic ester.

In the formation of an azulene, two moles of cyanoacetic ester takes part in this reaction with one mole of the troponoid, and even when the ester is reacted in the ratio of 1:1, the product is an azulene derivative formed by the reaction of 1:2 of the troponoid and the ester. As for the azulenes formed by this reaction, ethoxycarbonyl and cyano groups are either in 1- or 3-position, with hydroxyl or amino group in 2-position, giving numerous azulene derivatives with a variety of combinations.

In order to find out whether two moles of cyanoacetic ester reacts in the form of a dimer (CLXXI) in this reaction, its reaction with 2-chlorotropone was carried out but azulene derivatives could not be isolated at all, the reaction affording 1-oxa-2-azulanone derivative (CLXXII), 1-azaazulene derivative (CLXXIII), and a structurally unknown substance of m. p. 197°.[8]



From the foregoing experimental facts, it is considered that one mole of cyanoacetic ester reacts with one mole of troponoid to form a compound, which is much more reactive than the original troponoid and immediately reacts with the second mole of the reagent to form intermediates like (CLXXIVa) and (CLXXIVb), whose condensation, a kind of Ziegler condensation, forming a five-membered ring would give a bicyclic intermediate (CLXXVa) and (CLXXVb). By the polar effect of the carbonyl or imino group in the 2-position, and the attack of the ethoxycarbonyl or cyano group in 3-position by the ethoxide anion, this intermediate suffers cleavage of the C-C bond, through the third intermediates like (CLXXVIa) and (CLXXVIb), and forms the final products (CXVII, CXVIII, CXXIV, and CXXV). Such reaction results indicate the great driving force toward azulene-ring formation, giving azulene derivatives in one step without any intermediate product.

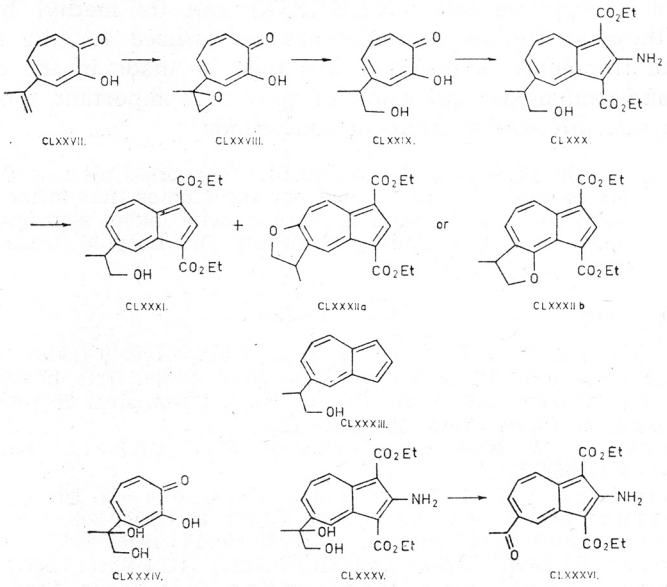


iv) *Attempted Syntheses of Azulene Precursor*

The new method for the syntheses of azulenes described in the foregoing section, are being applied to the attempted syntheses of lactaroviolin, a pigment of a kind of mushroom, and linderazulene, a dehydrogenation product of linderene, the component of *Lindera strychnifolia,* as the first step towards the synthesis of sesquiterpenes as natural azulenogen.

A new tropolone, which was named β-dolabrin (CLXXVII), was isolated during 1956 from the acid portion of the essential oil of *Thujopsis dolabrata,*[33] and this compound is used as the starting material for the above syntheses.

The epoxide (CLXXVIII) obtained from β-dolabrin is reduced to the primary alcohol, that is 9-hydroxyhinokitiol (CLXXIX), and its methyl ether is reacted with cyanoacetic ester, in the presence of an alkoxide, and orange yellow crystals (CLXXX), m. p. 118°, are obtained. Deamination of (CLXXX) with nitrous acid affords a minute amount of the deaminated compound (CLXXXI) and orange crystals of m. p. 86°, assumed to be (CLXXXIIa) or (CLXXXIIb). The deamination of the acetate of (CLXXX) affords the acetate of (CLXXXI), whose hydrolysis and subsequent decarboxylation gives an azulene derivative (CLXXXIII). The same treatment of glycol (CLXXXIV) obtained from the epoxide affords (CLXXXV), whose oxidation by periodic acid gives the 5-acetylazulene derivative (CLXXXVI). Attempt is now being made to synthesize natural azulenes from these compounds.[8]



IX. CONCLUSION

The new process for the syntheses of azulene derivatives developed in the laboratory of the writer is advantageous in that complicated azulene derivatives can be obtained in one step, in a good yield, by reaction at room temperature, although it requires the use of tropolones, which are still difficult to obtain. It may be said that, by the application of this new process, it

would be possible to synthesize various kinds azulene derivatives of the type now known for aromatic heterocyclic compounds. Among the azulenic compounds to be synthesized in future, there may be a number that would be found to have interesting biochemical activities, as well as biological, medical, and other applications. For this end, it is desirable that a more simple and advantageous process be found for the syntheses of troponoids.

It has been found recently that bicycloheptadiene (CLXXXVII), the condensation product of cyclopentadiene, a component of coal tar and acetylene, forms tropilidene (CLXXXVIII) merely by heating it to 470°.[34] When the dibromide of tropilidene is heated, it forms a tropylium cation (CLXXXIX)[35] and oxidation of tropilidene with potassium permanganate affords tropolone, though in a poor yield.[36]

CLXXXVII. CLXXXVIII. CLXXXIX.

Another interesting phenomenon revealed very recently is the fact that the application of an electron impact on toluene and xylene results in the entrance of one of the carbon atom in the side chain into the six-membered ring to form a tropylium cation (CLXXXIX) and its methyl homolog.[37] If and when these or similar processes can be utilized for the syntheses of tropones and tropolones, a progress will then be made in the chemistry of troponoids and azulenoids, and who can deny that important application will be found in this interesting group of compounds.

In conclusion, the present writer would like to express his sincere gratitude to the number of his co-workers who carried out the studies that formed the nucleus of this article and to many chemists abroad who have also given unfailing encouragement and interest, including Professor Dr. Leopold Ruzicka in whose honor this article is written.

REFERENCES

1. L. Ružička and F. A. Rudolph, *Helv. Chim. Acta* **9** (1926) 118.
2. (a) A. St. Pfau and Pl. A. Plattner, *Helv. Chim. Acta* **19** (1936) 858.
   (b) Pl. A. Plattner and A. St. Pfau, *Helv. Chim. Acta* **20** (1937) 224.
3. (a) M. Gordon, *Chem. Revs.* **50** (1952) 127.
   (b) W. Treibs, W. Kirchhof and W. Ziegenbein, *Fortschr. chem. Forsch.* **3** (1955) 334.
4. (a) K. Ziegler and K. Hafner, *Angew. Chem.* **67** (1955) 301.
   (b) K. Hafner and H. Welds, *Angew. Chem.* **67** (1955) 302.
5. (a) T. Nozoe, *Fortsch. Chem. org. Naturstoffe* **13** (1956) 232.
   (b) T. Nozoe, *Festschr. Arthur Stoll* (Birkhäuser AG.) Basel (1957) 746.
6. (a) T. Nozoe, S. Seto and S. Matsumura, *Proc. Japan Acad.* **28** (1952) 483.
   (b) S. Seto, *Science Repts. Tôhoku Univ.* I **37** (1953) 367.
7. J. W. Cook, J. D. Loudon and R. K. Razdan, *J. Chem. Soc.* **1954**, 4041.
8. T. Nozoe and co-workers, unpublished works.
9. Y. Kurita and M. Kubo, *J. Am. Chem. Soc.* in press.
10. I. Nitta and Y. Sasada, unpublished works.
11. Y. Miura, T. Noguchi and T. Nozoe, *Bull. soc. chim. biol.* **38** (1936) 1441.
12. K. Sato, unpublished results.
13. (a) T. Nozoe, S. Seto, S. Matsumura and T. Terasawa, *Chem. & Ind. (London)* **1954**, 1356.

(b) T. Nozoe, S. Seto, S. Matsumura and T. Terasawa, *Chem. & Ind. (London)* **1954**, 1357.
14. (a) T. Nozoe, S. Seto and S. Nozoe, *Proc. Japan Acad.* **32** (1956) 472.
(b) S. Seto and S. Nozoe, *Proc. Japan Acad.* **32** (1956) 765.
15. J. W. Cook, W. Graham, A. Cohen, R. W. Lapsley and C. A. Lawrence, *J. Chem. Soc.* **1944**, 322.
16. T. Nozoe, Y. Kitahara and T. Arai, *Proc. Japan Acad.* **30** (1954) 478.
17. (a) W. Treibs, R. Steinert and W. Kirchof, *Liebigs Ann. Chem.* **581** (1953) 54.
(b) A. G. Anderson and J. J. Tazuma, *J. Am. Chem. Soc.* **74** (1952) 3455.
18. E. Sebe and T. Matsumoto, unpublished work.
19. (a) T. Nozoe, T. Mukai, K. Takase, I. Murata and K. Matsumoto, *Proc. Japan Acad.* **29** (1953) 452.
(b) T. Nozoe, T. Mukai and I. Murata, *J. Am. Chem. Soc.* **76** (1954) 3352.
(c) T. Nozoe, T. Mukai and I. Murata, *Proc. Japan Acad.* **30** (1954) 482.
20. (a) H. Akino, K. Sato and Y. Suzuki, *Science Repts. Tôhoku Univ.* I **40** (1956) 92.
(b) H. Matsumura, *J. Chem. Soc. Japan* **77** (1956) 300.
(c) K. Kikuchi and T. Muroi, *J. Chem. Soc. Japan* **77** (1956) 1081.
(d) T. Muroi, *J. Chem. Soc. Japan* **77** (1956) 1084.
21. T. Nozoe, T. Ikemi and S. Ito, *Proc. Japan Acad.* **30** (1954) 609; *Science Repts. Tôhoku Univ.* I **38** (1954) 117.
22. J. P. Fourneau and I. Grundland, *Bull. soc. chim. France* **1955**, 1571.
23. T. Nozoe, M. Sato and T. Matsuda, *Science Repts. Tôhoku Univ.* I **37** (1953) 407.
24. T. Nozoe, M. Sato, S. Ito, K. Matsui and T. Matsuda, *Proc. Japan Acad.* **29** (1953) 565.
25. T. Nozoe, S. Ito and K. Matsui, *Proc. Japan Acad.* **30** (1954) 313.
26. T. Nozoe, S. Matsumura, Y. Murase and S. Seto, *Chem. & Ind. (London)* **1955**, 1257.
27. T. Nozoe, S. Seto, S. Matsumura and T. Asano, *Proc. Japan Acad.* **32** (1956) 339.
28. A. G. Anderson, J. A. Nelson and J. J. Tazuma, *J. Am. Chem. Soc.* **75** (1953) 4980.
29. W. H. Stafford et al., *Chem. & Ind. (London)* **1954**, 277; **1954**, 742.
30. W. E. Parham and H. E. Reiff, *J. Am. Chem. Soc.* **77** (1955) 1177.
31. S. Seto, *Science Repts. Tôhoku Univ.* I **37** (1953) 377.
32. Y. Kitahara, *Science Repts. Tôhoku Univ.* I **39** (1956) 250.
33. T. Nozoe, K. Takase and M. Ogata, *Chem. & Ind. (London)* in press.
34. Shell Chem. Corp.
35. (a) W. v. E. Doering and L. H. Knox, *J. Am. Chem. Soc.* **76** (1954) 3203.
(b) M. J. S. Dewar and R. Pettit, *Chem. & Ind. (London)* **1955**, 199.
36. W. v. E. Doering and L. H. Knox, *J. Am. Chem. Soc.* **72** (1950) 2305; **73** (1951) 828.
37. P. N. Rylander, S. Meyerson and H. M. Grubb, *J. Am. Chem. Soc.* **79** (1957) 842.

IZVOD

Sinteza azulenoida iz troponoida

Tetsuo Nozoe

Opisane su različite sinteze azulenskih derivata o kojima je povedena i diskusija. Istraživanja u autorovu laboratoriju pokazala su, da 2 - halotropon i tropolon metilni eter cikliziraju s guanidinom, tioureom, malonskim esterom i cijanoctenim esterom u peteročlane prstene i stvaraju brojne nove azulenske spojeve. Ovom metodom mogu se dobiti u jednom reakcionom stupnju, s dobrim iskorištenjem, i kod sobne temperature komplicirani azulenski derivati.

CHEMICAL INSTITUTE
TOHOKU UNIVERSITY
SENDAI, JAPAN

Primljeno 18. srpnja 1957.