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Polycyclic Azulenoid Systems

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The principal methods of synthesis of polycyclic azulene hydrocarbons and their derivatives are described and certain aspects of the practical applications of polycyclic azulenes are considered.
The bibliography includes 122 references.

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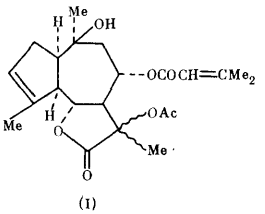
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I. INTRODUCTION

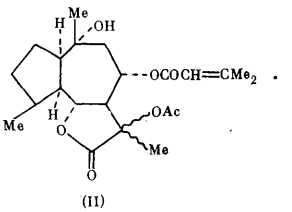
Azulene derivatives containing more than two condensed rings in the molecule have come to be called polycyclic azulenes. At the present time several tens of polycyclic azulenoid systems containing from three to seven condensed rings are known, many derivatives incorporating nitrogen-, sulphur-, and oxygen-containing heterocycles. To facilitate the description and nomenclature of polycyclic azulenes, we divided them into two subgroups: (1) carbocyclic azulenoid systems; (2) azulenes condensed with nitrogen-, sulphur-, and oxygen-containing heterocycles. The true heterocyclic analogues of azulenes as well as their π-electronic analogues—the so-called pseudoazulenes containing heteroatoms directly in one or both rings of the pseudoazulene nucleus—are not considered in this review because their number is very large and they might constitute the subject of a special review (see, for example, Timpe and Elcov[1]).

It is noteworthy that fully conjugated, i.e. dehydrogenated, polycyclic azulene hydrocarbons are not encountered in nature.

Only sesquiterpene precursors of polycyclic azulenes, usually incorporating saturated oxygen-containing heterocycles of the lactone type, are known. For example, the sesquiterpene derivatives (I) and (II) have been isolated from the extract of the roots of *Laserpitium silver*:

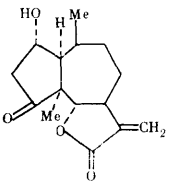


(I)

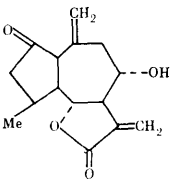


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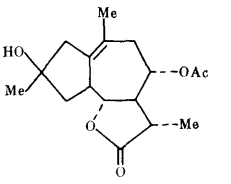
The structure of ivoxanthin (III)—a sesquiterpene lactone isolated from *Cyclachaena xanthifolia*[3], grossheimin (IV), isolated from *Grossheimia macrocephala*[4], and certain other sesquiterpenes [(V)–(VIII)] [5,6] which are in the main genetic precursors of guaiazulene and vetivazulene, have been established:



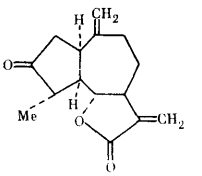
(III)



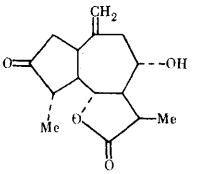
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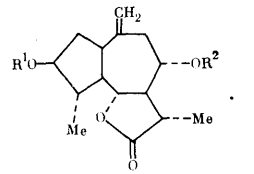
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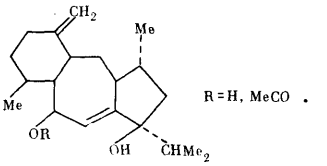


(VII)



(VIII)

The diterpene dolatriol (IX), which has the hydrocarbon skeleton of a hydrogenated precursor of 5,6-benzazulene, has been recently isolated from the tissues of molluscs[7]. Its structure was established by X-ray diffraction:



(IX)

The majority of carbocyclic azulenes have been considered[8] in connection with the discussion of a new approach to the concept of the aromaticity of conjugated cyclic hydrocarbons. The author bases his views on the concept of conjugated circuits recognised at the present time as significant structural elements characterising conjugated systems. The structures of conjugated hydrocarbons were investigated and circuits with an alternation of double and single C–C bonds were enumerated. Systems having only conjugated circuits of the $(4n + 2)$ type are defined as aromatic. Systems with conjugation contours only of the $(4n)$ type are regarded as antiaromatic, i.e. destabilised as a result of the delocalisation of the π electrons. Finally systems having circuits of both

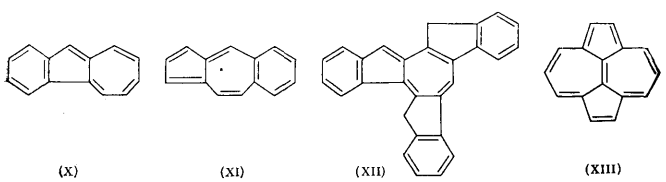
types simultaneously are classified as intermediate, manifesting only a partial aromatic character. This approach constitutes a logical extension to polycyclic systems of the famous Hückel (4*n* + 2) rule, which is rigorously applicable only to monocyclic systems. Furthermore, in the above study a brief comparison was made with several alternative schemes and their limitations were demonstrated[8].

Almost all polycyclic azulenes (particularly fully conjugated compounds) are high-melting readily crystallisable aromatic compounds. They are deeply coloured and frequently absorb light at longer wavelengths than the usual azulenes and their homologues and sometimes even in the near infrared. Isolated information concerning the synthesis of polycyclic azulenes is given in a number of reviews[9–11], but they do not provide a complete view of the state of affairs in this field, since they are devoted mainly to individual questions of synthesis or reactivity.

CARBOCYCLIC AZULENE DERIVATIVES

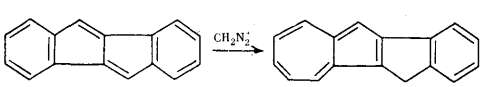
1. Expansion of the Benzene Ring of Azulene Precursors by Carbenes

The simplest tricyclic derivatives, namely the benzazulenes (X) and (XI), which are formed by the expansion of the benzene ring of fluorene and the corresponding indan derivative on treatment with an alkoxycarbonylcarbene, produced in its turn on thermal or catalytic decomposition of diazoacetic ester (the Buchner synthesis) with subsequent dehydrogenation and removal of the alkoxycarbonyl group, were obtained before other representatives of carbocyclic condensed systems[12–14].



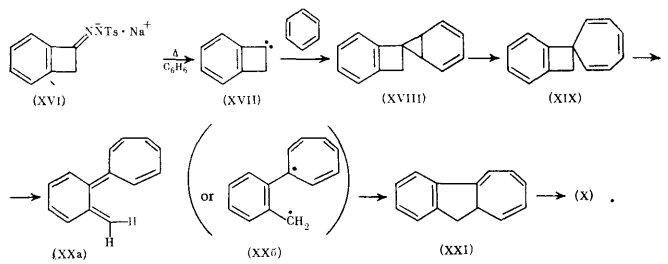
(X) (XI) (XII) (XIII)

Substituted 1,2-benzazulenes[15–18] as well as the heptacyclic azulene (XII)[19] and azupyrene (XIII),[20] which consists of a system of two condensed azulene nuclei, have been obtained analogously. The expansion of one of the benzene rings in 1,2 : 4,5-dibenzopentalene (XIV) leads to indeno[2,1-*a*]-azulene (XV):[21]



(XIV) (XV)

It has been shown recently that the thermolysis of the sodium salt of the tosylhydrazone of benzocyclobutenone (XVI) (a familiar method of synthesising carbenes[22]) in benzene gives rise to 9a,10-dihydrobenzo[*a*]azulene (XXI) in 30% yield. The synthesis of compound (XXI) can be represented as a result of the addition of benzocyclobutenylidene (XVII) to benzene with formation of spiro-norcaradiene (XVIII), which isomerises to spiro-cycloheptatriene (XIX). The ring opening of the benzocyclobutene part of compound (XIX) can lead to the *o*-quinodimethane derivatives (XXa) or to the equivalent biradical (XXb), which cyclises to compound (XIX). The dehydrogenation of compound (XXI) leads to benzo[*a*]azulene (X):[23]

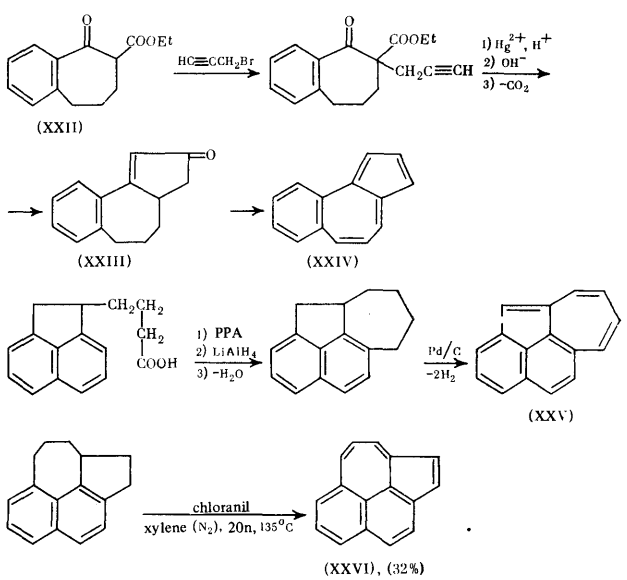


The methods described above are of great theoretical interest from the standpoint of the synthesis and study of new condensed azulenoid systems, but their preparative values is restricted by the low availability of the initial compounds and also by the low yields in the stages involving the expansion of the benzene ring and the dehydrogenation of the resulting precursors of azulene hydrocarbons. These methods have been significantly supplemented by syntheses which are based on the employment of non-azulenoid compounds as the starting materials, i.e. by another variety of the total synthesis.

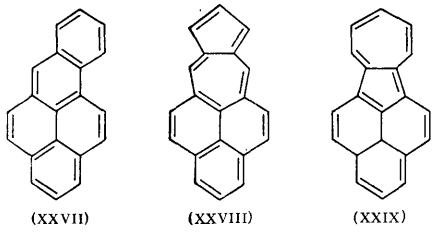
2. Total Synthesis of Carbocylic Derivatives of Azulene from Non-azulenoid Compounds

The total synthesis of polycyclic azulenes presupposes either the addition of a new five-membered ring to the complete seven-membered ring or conversely, at least one of the initial compounds must be condensed with at least one polymethylene, benzene, naphthalene, or another ring. The concluding stage is usually dehydrogenation.

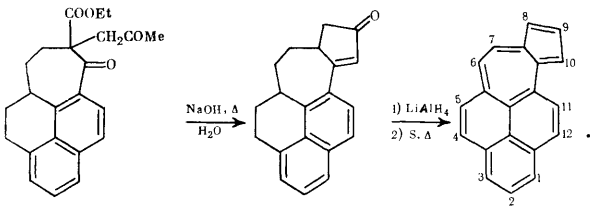
This method of synthesis of complex tri- and tetra-cyclic systems can be illustrated by the synthesis of 4,5-benzazulene (XXIV),[24] naphth[2,1,9,8-*ija*]azulene (XXV),[25] naphth[2,1,9,8-*cde*]azulene (XXVI),[26] and certain other derivatives:



In order to investigate the biological properties of polycyclic arenes and to compare them with the carcinogenic benzo[*a*]pyrene (XXVII), its non-alternant isomers were obtained: azuleno[5,6,7-*cd*]phenalene (XXVIII),[27] which exhibits a powerful carcinogenic activity, the weakly carcinogenic azulene[1,2,3-*cd*]phenalene (XXIX),[28] and azuleno-[4,5,6-*cd*]phenalene (XXX),[29] which, judging from the topology of its π-electron system [similarity to compound (XXVIII)] and its molecular structure [similarity to compound (XXVII)], should exhibit an appreciable biological activity:

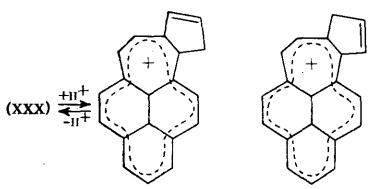


(XXVII) (XXVIII) (XXIX)



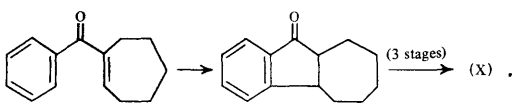
(XXX)

Compound (XXX) is distinctly basic and undergoes reversible protonation by trifluoroacetic acid, giving rise to a mixture of the cations (XXXIa) and (XXXIb) in proportions of 4 : 1:

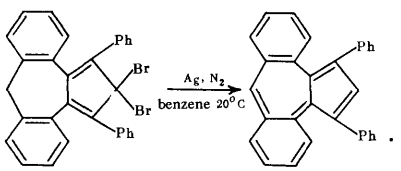


(XXXIa) (XXXIb)

An example of another method of closure of the five-membered ring is provided by the synthesis of 1,2-benzazulene [30–32]:

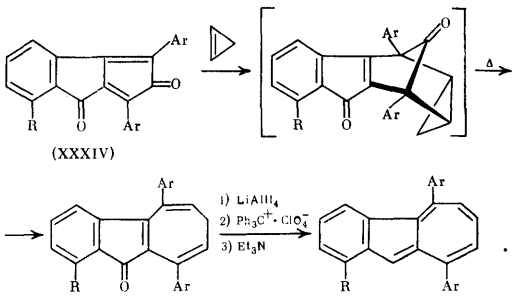


The synthesis of 1,3-diphenyldibenz[*eh*]azulene (XXXIII) by the dehydrobromination of the dibromo-derivative (XXXII) with silver dust in a nitrogen atmosphere was reported in 1974.[33] Compound (XXXIII) is stable only at temperatures not exceeding −18 °C (in a N_2 atmosphere).



(XXXII) (XXXIII)

The synthesis of substituted 1,2-benzazulenes from the "indanocyclone" (XXXIV) was included among those which involve the rearrangement of the five-membered ring to a seven-membered ring with subsequent reduction and dehydrogenation of the intermediates[34]:

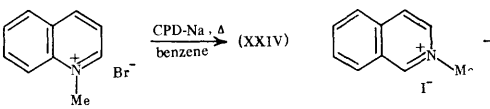


(XXXIV)

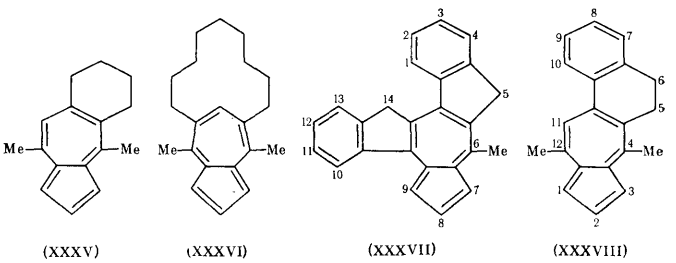
The methods examined have the advantage over those involving the expansion of the benzene ring in that they lead to final products with higher overall yields. However, they too are fairly cumbersome which reduces their preparative value compared with methods based on the cleavage of certain heterocyclic systems.

3. Quinolinium, Isoquinolinium, and Pyrylium Salts in the Synthesis of Polycyclic Azulenes

In contrast to pyridinium salts, quaternary quinolinium[35] and isoquinolinium[36] salts give rise to the corresponding benzazulenes (XXIV) and (XI) only in low yields on high-temperature condensation with cyclopentadienylsodium (CPD-Na):



There are at present almost no publications about the successful synthesis of polycyclic azulenes from benzopyrylium, isobenzopyrylium, and other condensed pyrylium derivatives. It is only known that tetrahydrobenz[*f*]azulene (XXXV) has been obtained from a tetrahydrobenzopyrylium salt and cyclopentadienylsodium is 3.3% yield[36] and that 4,8-dimethyl-5,7-nonamethyleneazulene (XXXVI) has been synthesised from the corresponding salt in 0.3% yield[37].



(XXXV) (XXXVI) (XXXVII) (XXXVIII)

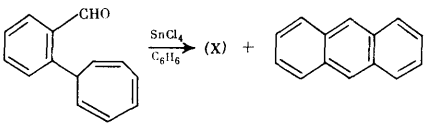
The deficiencies of the above syntheses are extremely low yields and the low availability of the initial salts, for example, in the second case. However, despite the fact that the methods have been as yet hardly elaborated, their possibilities are probably very considerable. It has been established recently that 2-methyldi-indeno[2,3;2',3'-*c*;*e*]pyrylium perchlorate, obtained by the method of Zhdanov et al.[38], reacts

with cyclopentadienylsodium to form 6-methyldi-indeno[3,2;;3',2'-*e*;*g*]azulene (XXXVIII) in 16% yield[39]. Under similar conditions, 2,10-dimethyl-3,4-dihydronaphtho[2,1-*c*]pyrylium perchlorate[40] gives rise to 4,12-dimethyl-5,6-dihydronaphth-[2,1-*f*]azulene (XXXVIII) in 22% yield[39]. The attempt to dehydrogenate compound (XXXVIII) by chloranil led merely to the product of "*ene*-synthesis", as in the reaction of *p*-benzoquinone with azulene[41].

When the initial substance contains a complete unsaturated seven-membered ring, the possibilities of the synthesis are greatly expanded. Such initial compounds may be, for example, derivatives of the cycloheptatriene and cycloheptafulvene series.

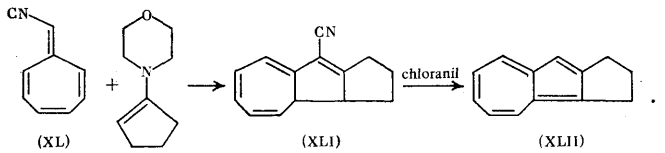
4. Syntheses based on Cycloheptatriene and Cycloheptafulvene Derivatives

Japanese investigators developed several methods for the synthesis of the five-membered ring of the azulene system from derivatives of the cycloheptatriene series, which lead to the formation of tri- and tetra-cyclic hydrocarbons. Thus, the catalytic intramolecular cyclisation of *o*-cycloheptatrienylbenzaldehyde (XXXIX) on treatment with $SnCl_4$ in benzene, leading to the formation of 1,2-benzazulene and anthracene, has been reported[42]:



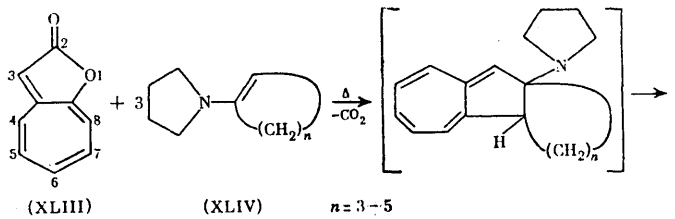
(XXXIX)

The condensation of 8-cyanocycloheptafulvene (XL) with morpholinocyclopentene leads to the formation of the dihydroazulene derivative (XLI), whose dehydrogenation yields 1-cyano-2,3-trimethyleneazulene (XLII):[43]

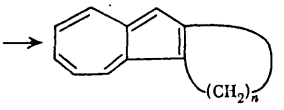


(XL) (XLI) (XLII)

It has been established[44] that 2*H*-cyclohepta[*b*]furan-2-one (XLIII), formed on condensation of equimolar amounts of 2-chlorotropone with sodiomalonic ester, also undergoes the cycloaddition reaction with enamines of type (XLIV) accompanied by the elimination of CO_2 and the amine, which leads to the formation of azulene derivatives (XLV):

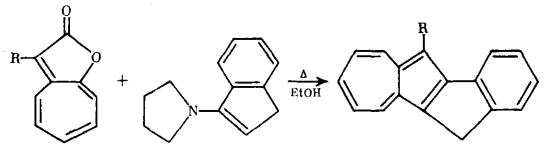


(XLIII) (XLIV) $n = 3-5$



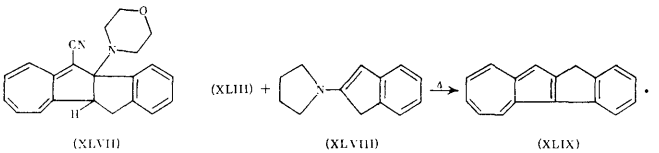
(XLV)

Heating of compound (XLIII), or its 3-cyano-derivative with 1-*N*-pyrrolidinoindene gives rise to indeno[2,1-*e*]azulene (XLVIa) or cyanoazulene (XLVIb) (yields 93 or 19% respectively):[45]



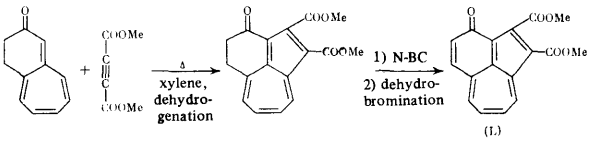
R = H (a), CN (b) (XLVI, a and b)

1-*N*-Morpholinoindene reacts with 3-cyano-2*H*-cyclohepta-[*b*]furan-2-one, forming 20% of compound (XLVIb) and 57% of the adduct (XLVII), which is converted quantitatively into compound (XLVIb) during chromatography on silica gel (eluent—benzene). The furanone (XLIII) reacts with 2-*N*-pyrrolidinoindene (XLVIII) much more slowly (140 h, 78 °C, alcohol), giving a 30% yield of indeno[1,2-*a*]azulene (XLIX), but compound (XLVIII) does not react with 3-cyanofuranone:



(XLVII) (XLVIII) (XLIX)

It was found that cycloheptafulvene derivatives can undergo the cycloaddition reaction with strong dienophiles, which led to the formation of the new tricyclic fully conjugated 3-*H*-benzo[*cd*]azulenone (L) system[46]:



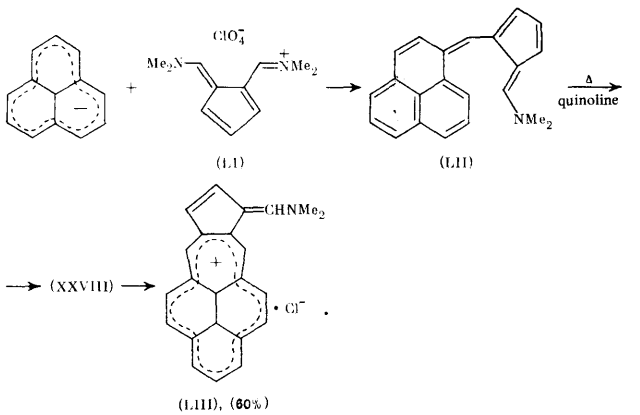
(L)

Presumably the scope for development of the above methods of synthesis may be inherent in the properties of the benzotropone and benzocycloheptafulvene derivatives (or other condensed systems of this type), but at the present time such data are not available.

5. Cyclisation of Polymethinium Salts and Fulvenes

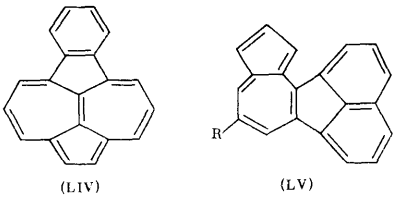
The cyclisation of fulvenes, developed by Ziegler and Hafner, is at present perhaps the most effective method of synthesis of azulenes[47,48]. This method proved to be effective also for the synthesis of polycyclic azulenes which are dfficult to obtain, such as, for example, azuleno[5,6,7-*cd*]-phenalene. The phenalene anion condenses with 6-dimethylamino-2-dimethylimmoniamethylfulvene perchlorate (LI) to form the enamine (LII), which can be converted into azuleno-[5,6,7-*cd*]phenalene by thermal cyclisation with elimination of dimethylamine[27]. Compound (XXVIII) is more basic than azulene and is extracted reversibly from benzene by 60%

H_3PO_4. When compound (XXVIII) is treated with the Vilsmeier reagent, the highly fluorescent salt (LIII) is formed:

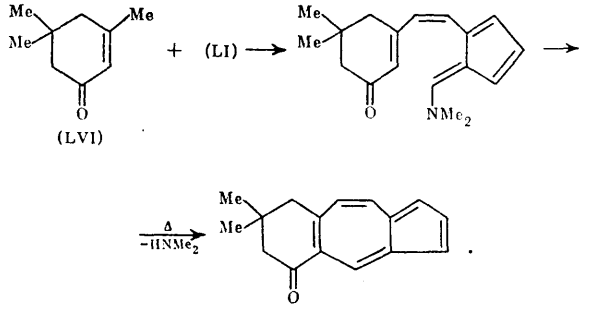


The carcinogenic azulene[5,6,7-*cd*]cyclopenta[*gh*]phenalene has been obtained similarly from the acephenalene anion[49].

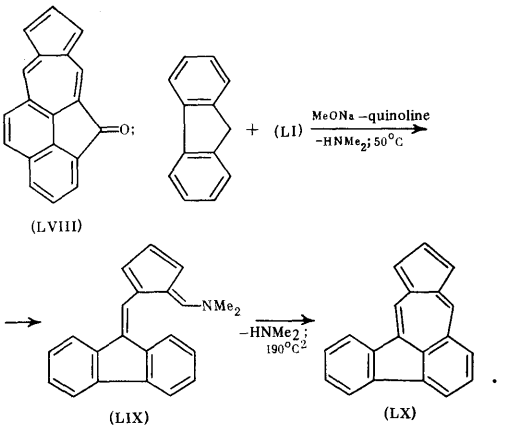
The cyclisation of fulvenes yielded azuleno[1,2,3-*cd*]-phenalene (XXIX) [28] and pyraceheptylene (XIII),[50] mentioned above, as well as benzopyraceheptylene (LIV) [50] and azuleno-[4,5-*a*]acenaphthylene (LV),[51] the mechanisms of the syntheses of which have been fully considered in a review[11].



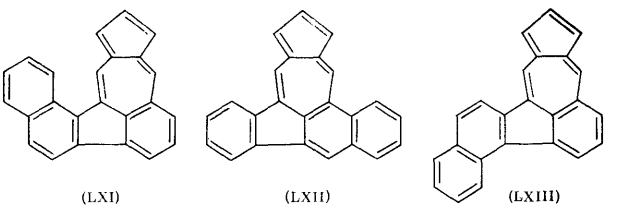
As in the synthesis of the azulene [5,6,7-*cd*]phenalene (XXVIII) system, the deprotonation of isophorone (LVI), in which the methyl group conjugated with the carbonyl group via the C=C bond reacts instead of the sterically hindered α-methylene group, leads to the formation of a stabilised allyl anion, which condenses with the heptamethinium salt (LI) to 7,7-dimethyl-5,6,7,8-tetrahydro[*f*]azulen-5-one (LVII) (yield 15%).[51]



Under similar conditions, 1-acenaphthenone condenses with compound (LI) to form a fulvenoid enaminoketone, which cyclises to azuleno[5,6,7-*cd*]acenaphthylen-6-one (LVIII) at 180 °C:[51]



The heptamethinium salt (LI) reacts similarly with fluorene to form the enamine (LIX), which undergoes ring closure at 190 °C to azuleno[5,6,7-*jk*]fluorene (LX) with elimination of dimethylamine. Benzofluorenes also condense with the salt (LXI), forming deeply coloured benzo-derivatives of the enamine (LIX), which can cyclise to the hexacyclic azulenes (LXI)–(LXIII). It has been established that only azulene-[5,6,7-*jk*]benzo[*a*]fluorene (LXI) is formed from benzo[*a*]-fluorene. However, the enamines formed from benzo[*b*]fluorene and benzo[*c*]fluorene can formally undergo ring closure via two different pathways, namely they can undergo annelation to the naphthalene or benzene nucleus of the benzofluorene system[51].



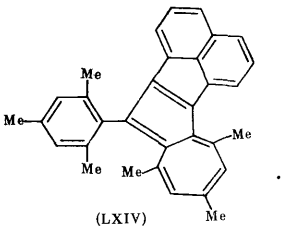
The azuleno[5,6,7-*jk*]benzo[*h*]fluorene (LXII) and azuleno-[5,6,7-*jk*]benzo[*c*]fluorene (LXIII) structures proposed by the authors[51] follow from the localisation energies L_r for the cyclisation reaction estimated by the Hückel method. In each case traces of the second isomer were detected. It is noteworthy that the theoretical evidence cannot replace, accordinto to the authors themselves, a rigorous chemical demonstration of structures (LXII) and (LXIII).

The cyclisation of polymethinium salts and fulvenes is one of the universal methods of synthesis of an extremely wide variety of highly condensed azulene hydrocarbons despite certain difficulties in the preparation of the initial and intermediate compounds. The scope of this method has been by no means fully exhausted, since, as will be shown below, other azulene derivatives readily enter into such reactions instead of fulvenes, cyclopentadienes, and other hydrocarbons.

6. Syntheses based on Acetylenic Compounds and Other Methods

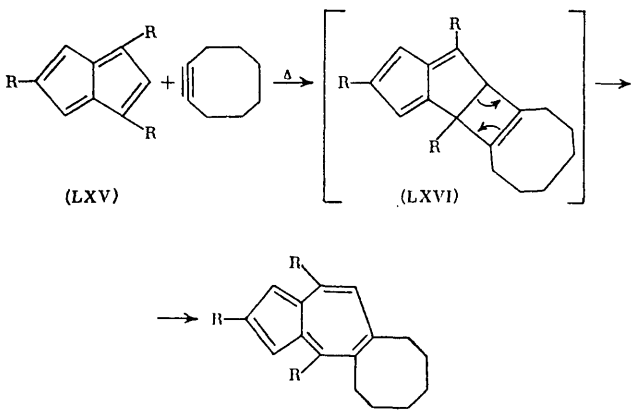
Among polycyclic fully conjugated azulenoid systems obtained from acetylene derivatives, only substituted acenaphthylenoazulene (LXIV), formed on irradiation of

diphenylperibisethynylnaphthalene, is known[52]:



(LXIV)

It has been observed[53] that the pentalene derivative (LXV) reacts at 270 °C with the highly strained triple bond of cyclo-octyne and it is tentatively suggested that this involves the intermediate formation of the cyclobutene derivative (LXVI), yielding 2,4,12-tri-t-butyl-5,6,7,8,9,10-hexahydrocyclo-octa[*f*]azulene (LXVII):

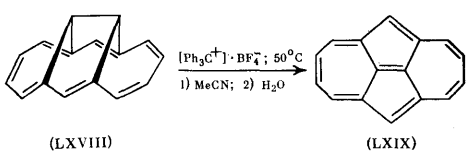


(LXV) (LXVI) (LXVII)

R = t-Bu .

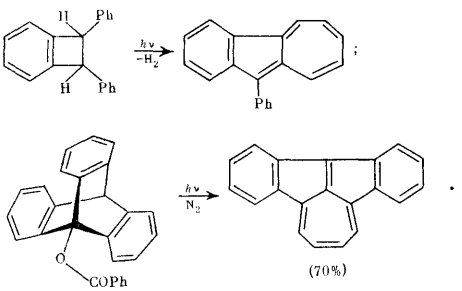
The exclusive formation of compound (LXVII) in 70% yield at such a high temperature indicates (in contrast to pentalene and methylpentalene) only a slight tendency of the 2,4,6-trisubstituted pentalene (LXV) to dimerise, i.e. the steric influence of bulky substituents.

An interesting reaction involves dehydrogenation of the non-polar 1,6,8,13-ethanediylidene[14]annulene (LXVIII) to dicyclohepta[*cd,gh*]pentalene (LXIX), which takes place under the influence of triphenylcarbonium tetrafluoroborate in 70% yield, has been discovered[54]. Compound (LXIX) is a new non-benzenoid isomer of pyrene:



(LXVIII) (LXIX)

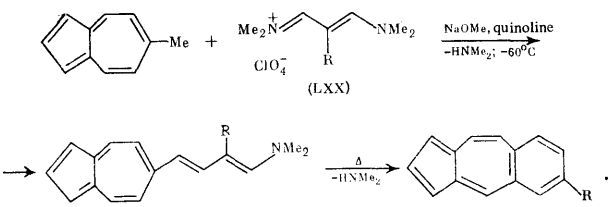
The photochemical isomerisation of 3,4-diphenyl-1,2-benzocyclobutene to 1-phenyl-2,3-benzazulene[55] and of benzoyloxytriptycene to benz[*a*]indeno[1,2,3-*cd*]azulene [56] has been described:



The fact that in the methods of synthesis described the azulene system is formed from the most "unexpected" precursors confirms its fairly high thermodynamic stability.

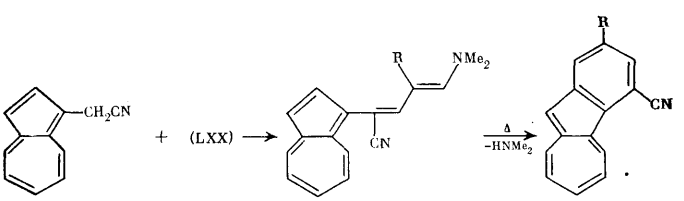
7. Derivatives of Azulenes as Starting Materials for the Synthesis of Polycyclic Systems

Many new and extremely varied polycyclic azulenoid systems have been obtained from comparatively simple azulene derivatives containing functional groups in the five-membered ring, seven-membered ring, or both rings simultaneously. The formation of the benzo-ring on the azulene system may be illustrated by the synthesis of 5,6-benzazulene and its derivatives[57]:



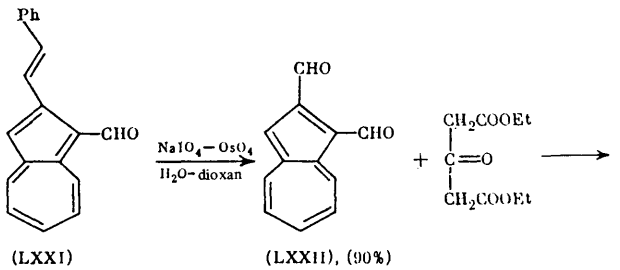
(LXX)

Here R = H, Et, Ph, $PhCH_2$, or OMe. The successful condensation of their trimethinium salt (LXXX) with the methyl group of 6-methylazulene is evidently due to the electron-accepting influence of the seven-membered ring of the azulene system, which leads to an increase of the mobility of the methyl protons. The authors[57] used the mobility of the methylene protons in 1-azulenylacetonitrile to achieve the formation of a similar 1,2-benzo-ring:

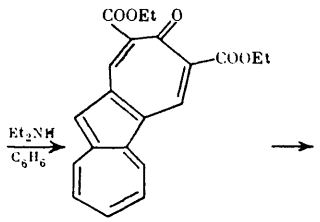


The corresponding functional derivatives of azulene, for example, 1,2-diformylazulene (LXXII), obtained[58] from 2-styrylazulene-1-aldehyde (LXXI) by the Lemieux–Johnson oxidation, are very convenient for the formation of new rings condensed with the 1- and 2-positions of the azulene nucleus. Subsequent condensation of the dialdehyde (LXXII) with acetonedicarboxylic ester, hydrolysis, and decarboxylation

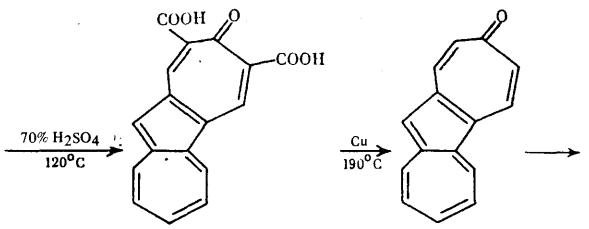
lead to azuleno[1,2-*d*]tropone (LXXIII):[58]



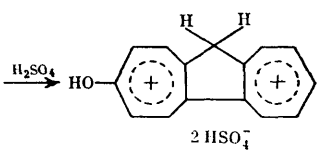
(LXXI) (LXXII), (90%)



(58%)



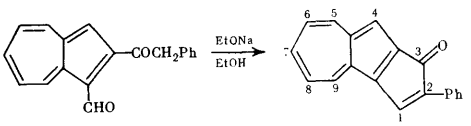
(LXXIII), (31%)



(LXXIV)

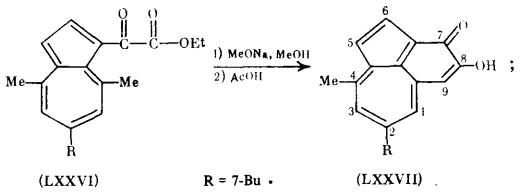
Azulenotropone (LXXIII) dissolves in H_2SO_4 with formation of the doubly charged cation (LXXIV).

Another example of the utilisation of a 1,2-dicarbonyl derivative of azulene is the synthesis of 2-phenylazuleno-[1,2-d]cyclopentadien-3-one (LXXV):[59]



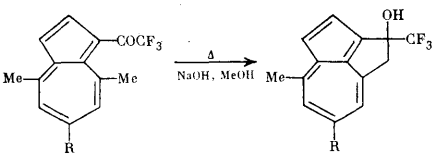
(LXXV).

In those compounds where the functional groups or substituents reacting with one another are located in different rings of the azulene system, for example, in the 1- and 8-positions, intramolecular condensation leads to a closer condensation of the newly formed ring with the azulene nucleus. Thus ethyl 6-t-butyl-4,8-dimethyl-1-azulenyl glyoxylate (LXXVI) cyclises to 2-t-butyl-8-hydroxy-4-methyl-7*H*-benz[*cd*]azulen-7-one (LXXVII) on treatment with sodium methoxide[60]:



(LXXVI) R = 7-Bu . (LXXVII)

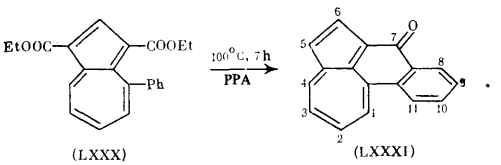
The analogous treatment of 1-trifluoroacetyl derivatives of 4,6,8-trimethylazulene (LXXVIIIa)[61] or 4,8-dimethyl-6-styrylazulene (LXXVIIIb)[39] results in the formation of the corresponding stable tertiary alcohols—derivatives of dihydroaceazulene (LXXIX, a and b):



(LXXVIII, a and b) (LXXIX, a and b)

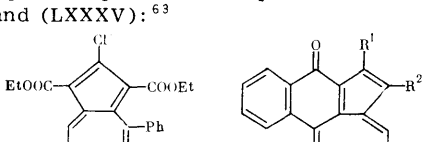
R = Me (a), —CH=CH—Ph (b) .

The intramolecular cyclisation of diethyl 4-phenylazulene-1,3-dicarboxylate (LXXX) has been achieved[62] in polyphosphoric acid (PPA) with formation of a new heterocyclic system—7*H*-naph[3,2,1-cd]azulen-7-one (LXXXI), which is the azulene analogue of benzanthrone:



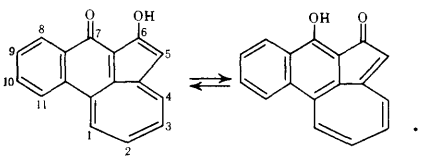
(LXXX) (LXXXI)

The cyclisation of the 2-chloro-derivative (LXXXII) at 100 °C for 3 h in polyphosphoric acid results in the formation of all three possible products—compounds (LXXXIII), (LXXIV), and (LXXXV):[63]



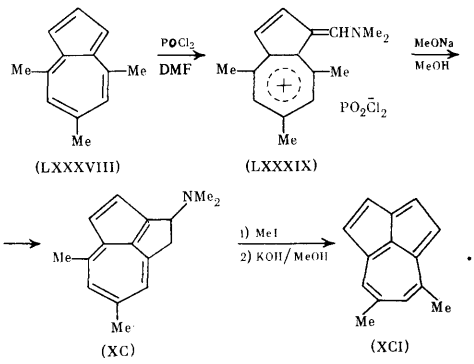
(LXXXII) (LXXXIII): R^1 = Cl, R^2 = H;
(LXXXIV): R^1 = Cl, R^2 = COOEt;
(LXXXV): R^1 = H, R^2 = COOEt .

The ethoxycarbonyl group can be eliminated from compound (LXXXIV) and the latter can exchange its chlorine for the methoxy-group: the demethylation of the intermediate methoxy-derivative yields 6-hydroxy-7*H*-naphth[3,2,1-*cd*]azulen-7-one (LXXXVI), which exists in tautomeric equilibrium with compound [LXXXVII]:



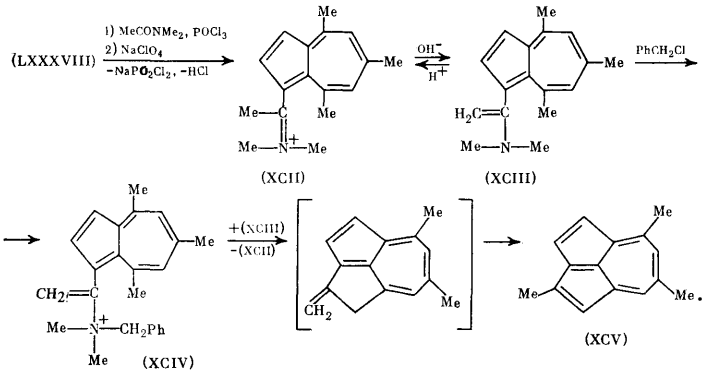
(LXXXVI) (LXXXVII)

The mobility of the hydrogen atoms in the methyl groups of 4,6,8-trimethylazulene enabled Hafner and Schneider[64] to achieve the closure of the five-membered ring condensed along the *cd* faces of the azulene nucleus, which ultimately led to the formation of a new tricyclic conjugated system—aceazulene (XCI):

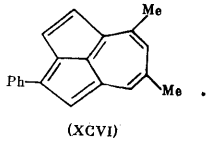


Like acenaphthylene, compound (XCI) is not aromatic; it is stable only at temperatures below 77 °C.

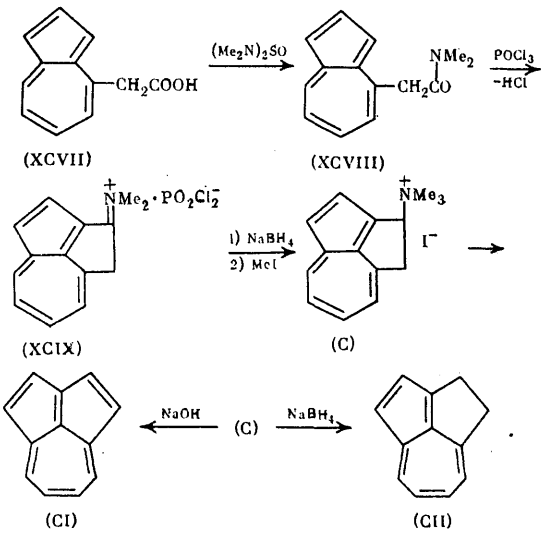
In the Vilsmeier acetylation of compound (LXXXVIII), the immonium salt (XCII) formed initially does not hydrolyse immediately to an acetyl derivative when rendered alkaline but gives rise to the enamine (XCIII). Treatment of the latter with benzyl chloride results in the intermediate formation of a quaternary ammonium salt (XCIV), which undergoes the Hofmann cleavage on treatment with an excess of the enamine (XCIII), accompanied by the closure of a new five-membered ring with formation of the aceazulene derivative (XCV):[65]



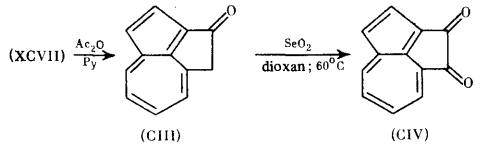
The Vilsmeier benzoylation of compound (LXXXVIII) also results in the formation of the corresponding aceazulene derivative (XCVI) in addition to the main reaction product (the 1-benzoyl derivative):



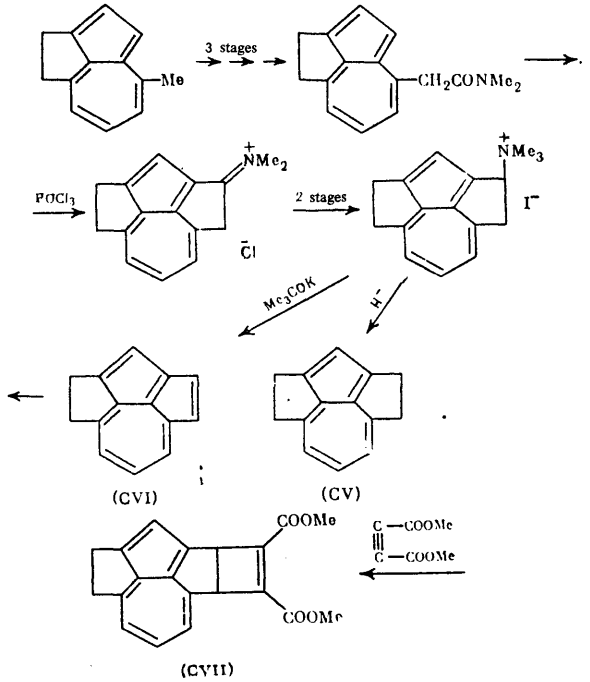
The unsubstituted cyclopent[*cd*]azulene (CI) was obtained from azulene-4-acetic acid (XCVII) as a result of a series of successive transformations[66]:



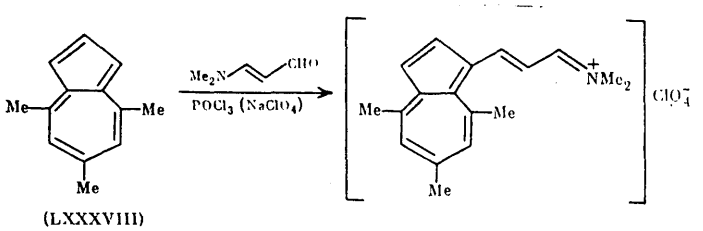
Direct cyclisation of compound (XCVII) in acetic anhydride in the presence of pyridine leads to the formation of the 2-oxo-derivative (CIII), whose oxidation with selenium dioxide in dioxan (60 °C, 3 h) yielded cyclopent[*cd*]azulene-1,2-dione (CIV)—a non-benzenoid isomer of acenaphthenequinone[66]:



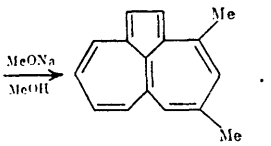
Using the scheme indicated below, Hafner et al.[66] obtained 1,2,6,7-tetrahydrodicyclopent[*cd;ij*]azulene (CV) and 1,2-dihydrodicyclopent[*cd;ij*]azulene (CVI); the latter is capable of undergoing the cycloaddition reaction with dimethyl acetylenedicarboxylate via one of the double bonds of the cyclopentane ring, forming the adduct (CVII):



Hafner and Schneider[64] obtained for the first time from 4,6,8-trimethylazulene (TMA) a new stable aromatic system—3,5-dimethylaceheptylene (CVIII):

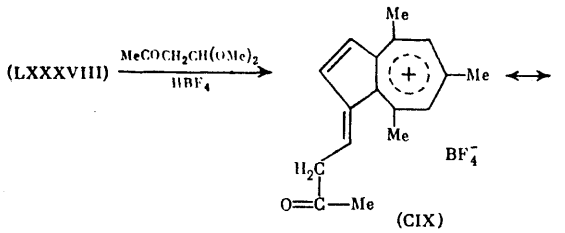


(LXXXVIII)

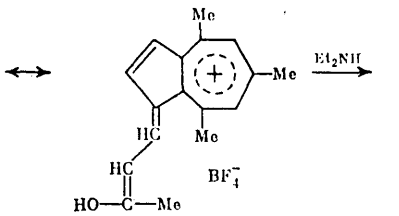


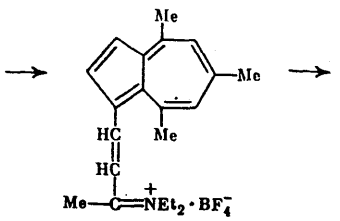
(CVIII)

If formylacetone acetal in a strongly acid medium is used instead of β-dimethylaminoacroleine, then the intermediate azulenylium salt (CIX) is cleaved after treatment with diethylamine and subsequent heating with sodium ethoxide to form 3,5,8-trimethylaceheptylene (CX):[67]



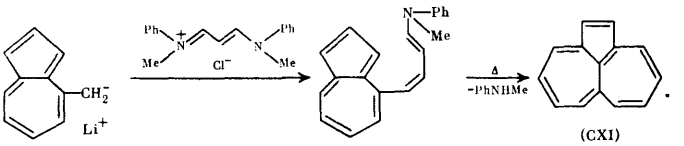
(CIX)





(CX)

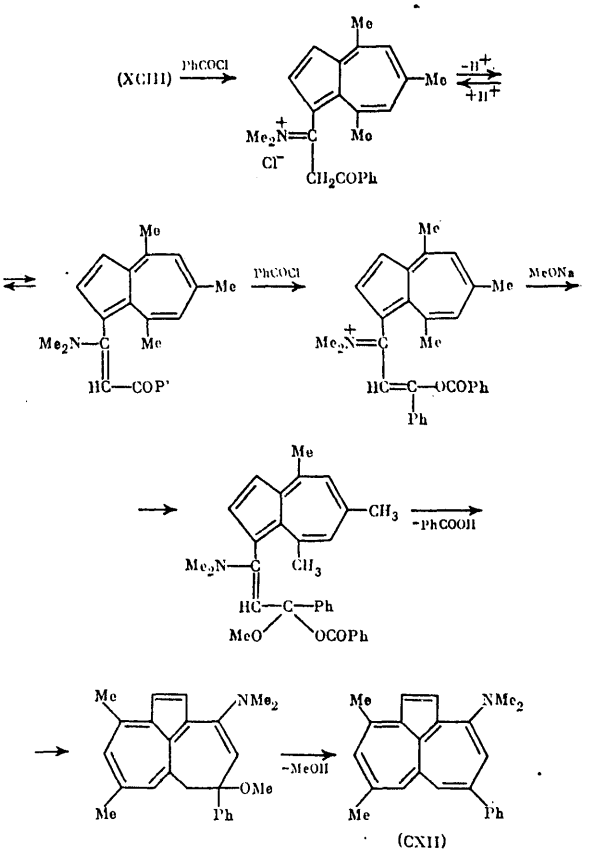
The unsubstituted aceheptylene (CXI) has been obtained by the intramolecular cyclisation of 1-(4-azulenyl)-4-methylphenylaminobutadiene[68]:



(CXI)

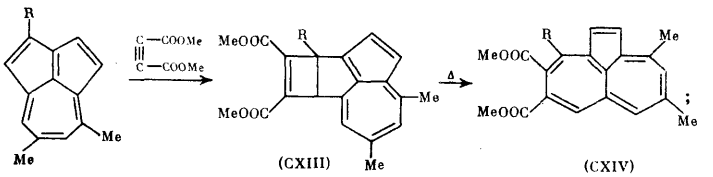
This method has been extended[57] to guaiazulene, from which a series of substitued aceheptylenes were obtained. Similar substituted derivatives have also been synthesised by the same workers from 4-methylazulene.

3,5-Dimethyl-10-dimethylamino-8-phenylaceheptylene (CXII) has been obtained by the benzoylation of the enamine (XCIII) in a series of successive stages[65]:



(CXII)

Derivatives of aceheptylene can be obtained also by the cycloaddition reaction of cyclopent[*cd*]azulenes with acetylenedicarboxylic esters followed by thermal isomerisation of the adduct (CXIV):[69]

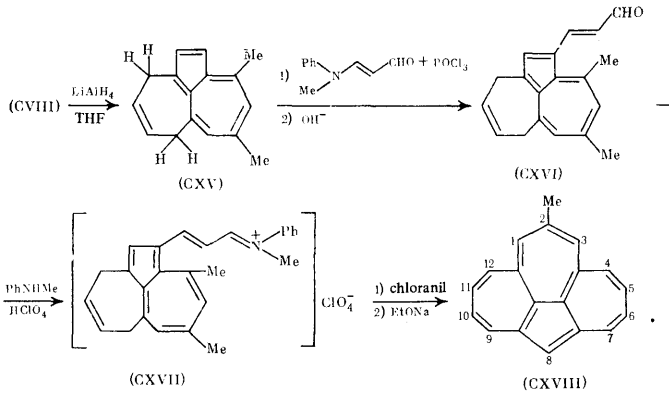


(CXIII) (CXIV)

R = H, Me, Ph .

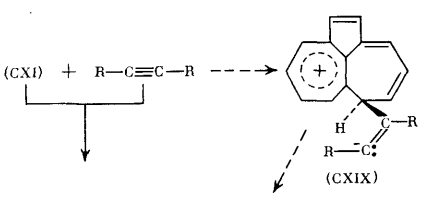
It has been established[70] that the aceheptylene derivative (CVIII) is reduced to the dihydro-derivative (CXV) on treatment with lithium tetrahydroaluminate. The involvement of

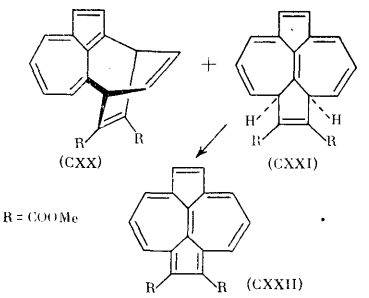
compound (CXV) in the Vilsmeier reaction ($POCl_3$ + β-methylphenylaminoacroleine) leads to the aldehyde (CXVI), which reacts with *N*-methylaniline in the presence of $HClO_4$ to form the immonium salt (CXVII). Dehydrogenation of the salt obtained with chloranil and subsequent cyclisation in the presence of bases lead to a new tetracyclic conjugated azulenoid system—2-methylazuleno[8,8a,1,2-*def*]heptalene (CXVIII):[70]



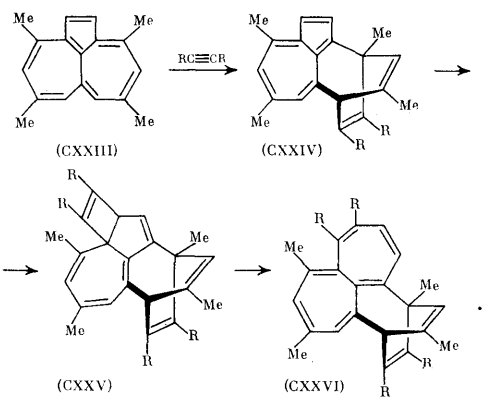
Pentalene[53], azulene, cyclopent[*cd*]azulene[71], and the readily available aceheptylene (CXI) [72] undergo cycloaddition reactions with activated alkynes unusually readily with formation of new polycyclic systems[73]. When compound (CXI) is heated for 1 h with dimethyl acetylenecarboxylate in 1 : 1 molar proportions in boiling tetralin, it is possible to obtain, together with the Diels–Alder adduct (CXX) (in 1% yield), also a 25% yield of 1,2-dicyclopenta[*ef*,*kl*]heptalenedicarboxylic ester (CXXII). The latter is probably formed from the primary adduct (CXXI), which can be obtained, like compound (CXX), from the intermediate dipolar compound (CXIX), arising either from the attack of the electron-accepting alkyne on the position with the highest electron density in the molecule of compound (CXI) or by virtue of a synchronous cycloaddition.

3,5-Dimethylaceheptylene and 3,5,8,10-tetramethylaceheptylene (CXXIII) react with acetylenic esters like compound (CXI).[70] However, in these cases the formation of a Diels–Alder adduct of type (CXX) predominates. The tetracyclic system on which compound (CXXII) is based had been obtained earlier only by a multistage procedure with an extremely low overall yield[74]. Within the limits of the possible comparison, the spectroscopic properties of compound (CXXII) are consistent with those of the unsubstituted tetracyclic hydrocarbon:



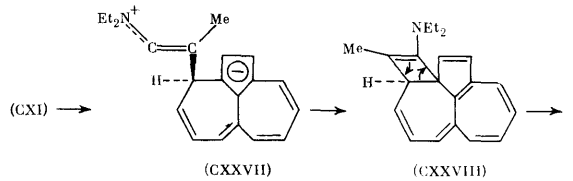


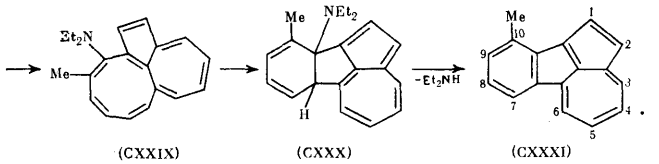
Like azulene, Diels–Alder adducts of type (CXX) undergo a dipolar cycloaddition reaction with acetylenedicarboxylic ester at 200 °C in the 1,8a-positions of the azulenoid component of compound (CXX). Thus, 3,5,8,10-tetramethylaceheptylene, which is more enriched in electrons compared with compound (CXI), reacts with acetylenedicarboxylic ester in molar proportions of 1 : 2 to form the 3,5,8,10-tetramethyl derivative (CXXV) (3%), the Diels–Alder adduct (CXXIV) (26%), and the thermally stable diene adduct of cyclohepta[*ef*]heptalene (CXXVI) (12%):



The primary formation of the 1 : 1 adduct (CXXIV) is followed by a secondary cycloaddition with formation of the adduct (CXXV), whose valence isomerisation, accompanied by the opening of the cyclobutene ring, leads to the formation of compound (CXXVI).

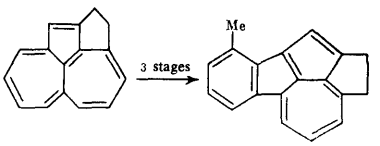
Aceheptylene (CXI) and its derivatives also undergo the cycloaddition reaction (involving very high yields) with ynamines, but the alkyne, which has an enhanced electron density, initially attacks the position most depleted in electrons. The reaction of (CXI) with *N*,*N*-diethyl-1-propynylamine probably proceeds via the formation of the intermediate (CXXVII) and the cyclic adduct (CXXVIII). The reaction involving the expansion of the cyclobutene ring leads to the thermally unstable cyclonon[*cd*]azulene derivative (CXXIX), whose valence isomerisation to compound (CXXX) and subsequent elimination of diethylamine give a 75% yield of 10-methylbenzo[*a*]cyclopent[*cd*]azulene (CXXXI)—a non-benzenoid analogue of fluoranthene, which cannot be obtained by other methods:





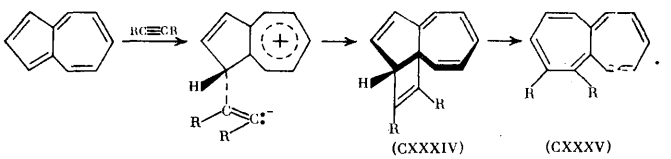
(CXXIX) (CXXX) (CXXXI)

3,5-Dimethyl- and 3,5,8,10-tetramethyl-aceheptylenes react with *N*,*N*-diethyl-1-propynylamine to form 3,5-dimethyl- and 3,5,7,9-tetramethyl-derivatives of the hydrocarbon (CXXXI) in yields of 68 and 92% respectively. A tetracyclic hydrocarbon (CXXXII), for example, can be converted by an analogous procedure into 4,9-dimethyl-1,2-dihydrobenzo-[1,2]dicyclopent[*cd*,*ij*]azulene (CXXXIII) in 21% yield[73]:



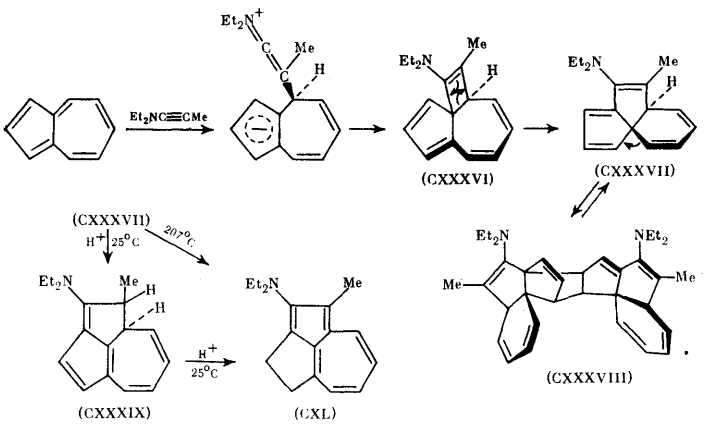
(CXXXII) (CXXXIII)

It is known that azulene can not only undergo substitutional addition reactions with electron-deficient alkynes (for example with dimethyl acetylenedicarboxylate)[75] but also, like electron-enriched alkenes, the thermally induced dipolar cycloaddition via the five-membered ring of the azulene nucleus, the valence isomerisation of the primary adduct (CXXXIV) yielding the heptalene derivative (CXXXV), which is the nearest higher homologue of azulene[53]:



(CXXXIV) (CXXXV)

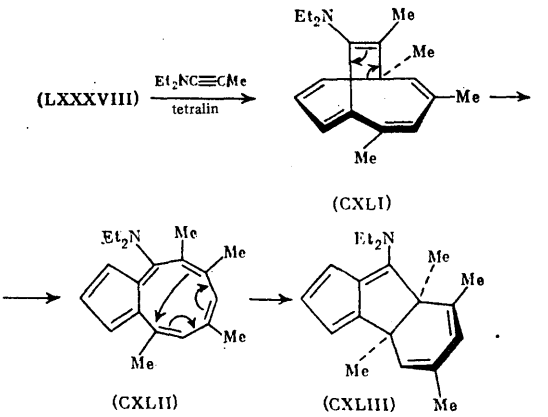
An attempt to make azulene react with *N*,*N*-diethyl-1-propynylamine led to the rapid formation of a 1 : 1 adduct (CXXXVII) in 83% yield[76]. In its crystalline form the bridged spiro-[4,5]decatetraene (CXXXVII) exists in the form of the dimer (CXXXVIII) by virtue of the [4 + 2]cycloaddition of its cyclopentadiene components, while in solution (in benzene and CCl_4 as solvents) the retrodiene synthesis takes place rapidly. Compound (CXXXVII) can be formed via the primary adduct (CXXXVI), which contains the structural element of spiro-[3,4]octa-1,5,7-triene, which readily undergoes[77] 1,5-sigmatropic ring expansion with formation of the dihydropentalene derivative (CXXXIX). The latter is converted into the more stable form (CXL) in 80% yield after 3 h under the conditions of the formation reaction of compound (CXXXIX):



(CXXXVI) (CXXXVII) (CXXXVIII) (CXXXIX) (CXL)

The reaction of azulene with *N*,*N*-diethyl-1-propynylamine in boilbing tetralin gives rise immediately to compound (CXL) in 17% yield, probably also via compound (CXXXVII) as an intermediate stage.

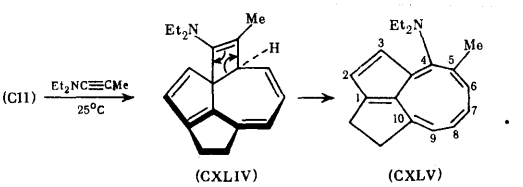
Compound (LXXXVIII) reacts with propynylamine only in boiling tetralin, the cycloaddition being hindered by the alkyl groups in the 4- and 8-positions:



(CXLI) (CXLII) (CXLIII)

The main product proved to be the dihydrocyclopentindene (CXLIII) obtained in 15% yield and containing the resonance-stabilised aminofulvene component. The intermediate state (CXLI), which is incapable of the 1,5-sigmatropic ring expansion owing to the steric hindrance due to the methyl groups but undergoes valence isomerisation to the unstable cyclononatetraene derivative (CXLII), is postulated in this thermally induced reaction. Valence isomerisation is characteristic of cyclononatetraene derivatives[78] and leads to the thermally stable system (CXLIII).

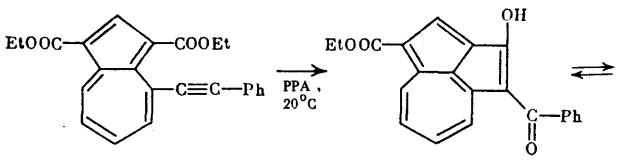
The bridged azulene (CII) reacts with propynylamine even at room temperature with formation of the red-brown crystalline derivative 4-diethynylamino-5-methylcyclopentacyclononatetraene (CXLV) in 47% yield[79]:



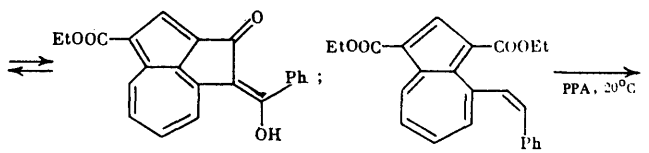
(CXLIV) (CXLV)

The conformation of the nine-membered ring in compound (CXLV) is close to the boat conformation in cyclo-octatetraene.

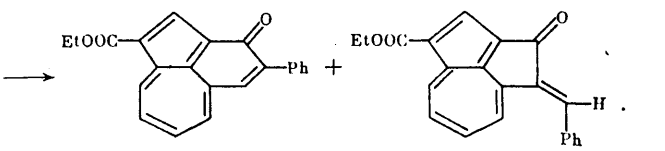
It has been shown recently[80] that diethyl 4-phenylethynylazulene-1,3-dicarboxylate (CXLVI) undergoes intramolecular cyclisation under the conditions of a reaction of the Friedel–Crafts type (treatment with polyphosphoric acid) with formation of the cyclopent[*cd*]azulene derivative (CXLVII).[81] Similarly diethyl-4-styrylazulene-1,3-dicarboxylate (CXLVIII) forms derivatives of benz[*cd*]azulene (CXLIX) and cyclopent-[*cd*]azulene (CL):



(CXLVI) (CXLVII)

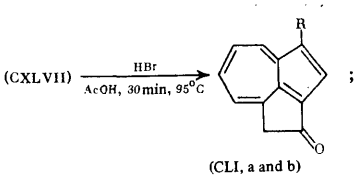


(CXLVIII)



(CXLIX) (CL)

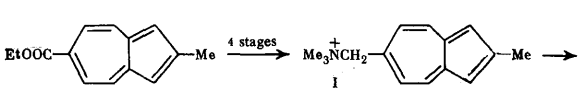
Treatment of compound (CXLVII) with 48% hydrobromic acid in acetic acid leads to the formation of the products of the elimination of the benzoyl and partly the ethoxycarbonyl groups [compounds (CLI, a and b)]:



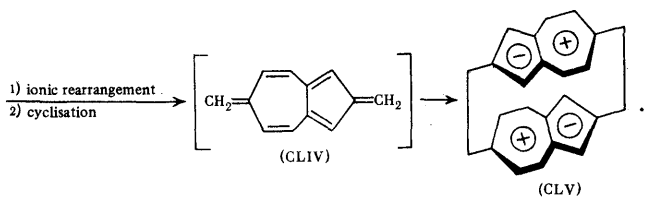
(CLI, a and b)

R = H (a), COOEt (b) .

The multiplicity of the polycyclic azulenoid systems obtained from simple azulenes with functional groups is not exhausted merely by planar conjugated molecules. In 1976 American workers[82] obtained the first azulene-containing macrocyclic system of *anti*-[2.2](2,6)azulenophane (CLV) from 6-ethoxycarbonyl-2-methylazulene synthesised in 8 stages from propiophenone:



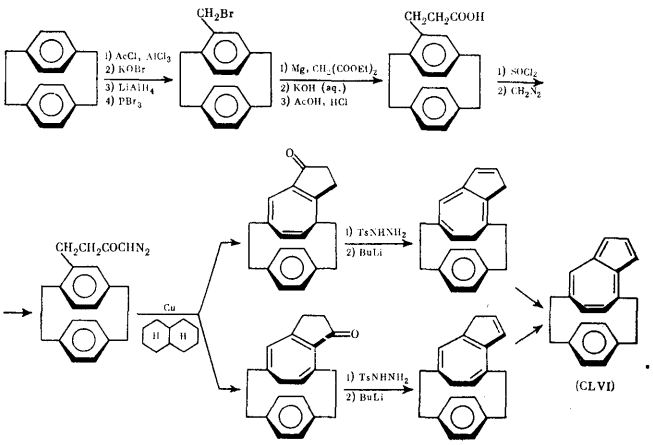
(CLII) (CLIII)



(CLIV) (CLV)

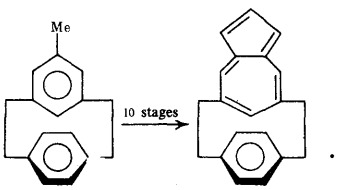
The structure of the cyclophane was demonstrated by electronic spectroscopy and ^{1}H NMR and also mass-spectrometry. Somewhat later, at the end of 1976, Japanese workers published yet another method of synthesis of the azulenocyclophane (CLV), illustrating the extensive possibilities of the intermediate transformations of azulene derivatives[83]. The protonation and electrophilic substitution of the azulenophane (CLV) by tetracyanoethylene have been recently investigated[84].

The syntheses of two types of [2.2]paracycloazulenophanes, (CLVI) and (CLVIII),[85] obtained by an intramolecular reaction involving the insertion of a carbene in [2.2]cyclophanes, have been published:



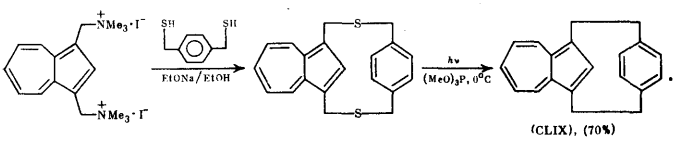
(CLVI)

[2.2]Paracyclo(5,7)azulenophane (CLVIII) was obtained from 5-methyl[2.2]metaparacyclophane (CLVII) by a simpler procedure with an overall yield of approximately 2%:



(CLVII) (CLVIII), (2%)

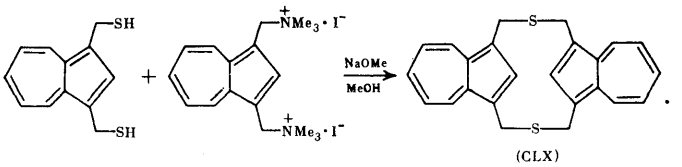
Simultaneously with the compounds indicated above, [2](1,3)azuleno[2]paracyclophane (CLIX) was also obtained[86]:



(CLIX), (70%)

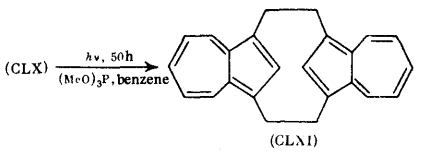
The condensation of 1,3-di(mercaptomethyl)azulene with 1,3-di(methyltrimethylammonia)azulene di-iodide in dry methanol with NaOMe (a high dilution technique is used) gives a

54% yield of 2,13-dithia[3.3]azulenophane (CLX):[87]



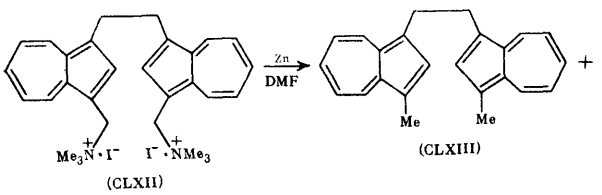
(CLX)

The photodesulphurisation of compound (CLX) in solution in trimethylphosphite–benzene gives rise to [2.2](1,3)-azulenophane (CLXI) in 16% yield:

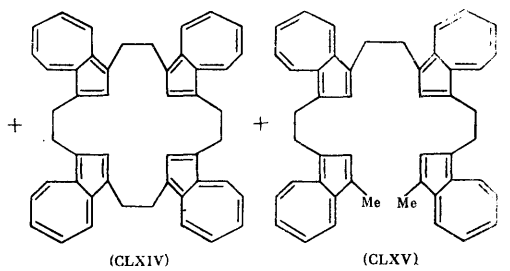


(CLXI)

Treatment of compound (CLXII) with zinc dust in dimethylformamide (DMF) under the conditions of high dilution leads mainly to polymeric products, but 3,3-diazulenyl-1,1-dimethylethane (CLXIII), [2.2.2.2](1,3)azulenophane (CLXIV), and an azulene tetramer with the structure (CLXV) have been isolated chromatographically in yields of 7, 0.1, and 1% respectively[88]:

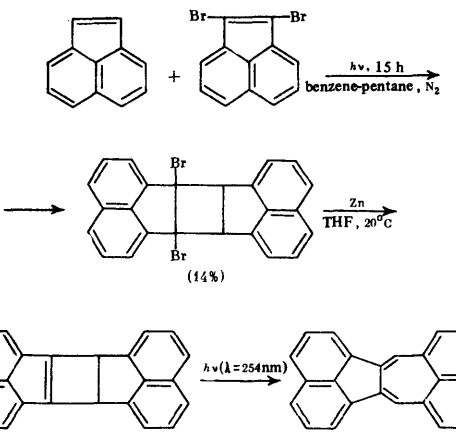


(CLXII) (CLXIII)



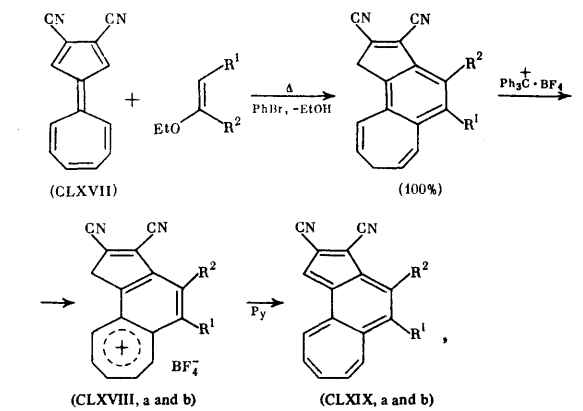
(CLXIV) (CLXV)

The extensive synthetic possibilities of the utilisation of azulene derivatives with functional groups are not exhausted by the carbocyclic systems presented here. Methods of synthesising polycyclic systems with condensed heterocyclic nuclei will be considered below. Before proceeding to these compounds, mention should probably be made of individual representatives of the kind of "non-classical azulenoid systems" obtained recently, in which the role of the seven-membered ring is assumed by another conjugated system, whose structure does not resemble that of the tropylium cation but which is capable of carrying a partial positive charge delocalised over the system. The hydrocarbon (CLXVI), obtained by a combination of photochemical and chemical methods[89], can serve as a representative of such "non-classical systems":



(14%) (CLXVI).

Stable derivatives of phenazulene (CLXIX, a and b), obtained by the [12 + 2] addition of ethoxycyclohexene or α-ethoxystyrene to 8,9-dicyanosesquifulvalene (CLXVII), have an intense blue-violet colour and are very weakly basic, but are protonated by concentrated H_2SO_4 in acetic acid to compounds (CLXVIII, a and b):[90]

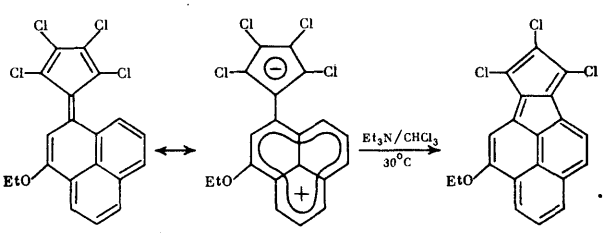


(CLXVII) (100%)

(CLXVIII, a and b) (CLXIX, a and b)

$R^1+R^2=-(CH_2)_4-$ (a), $R^1=H$, $R^2=C_6H_5$ (b).

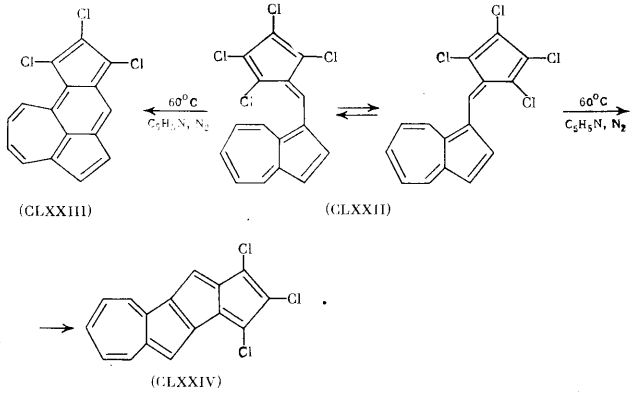
Japanese workers have reported[91,92] that the dehydrochlorination of 9,10,11,12-tetrachloro-2-ethoxypentaphenafulvalene (CLXX) by triethylamine leads to a new pentacyclic conjugated system—6,7,8-trichloro-4-ethoxypentaleno[1,2,3-*cd*]phenalene (CLXXI):



(CLXX) (CLXXI)

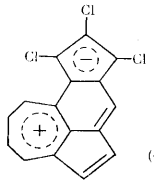
Depending on the nature of the solvent, the ring closure reaction takes place in acetone and n-heptane in 45 min and 10 h respectively. On the basis of these data, the authors proposed an ionic reaction mechanism. If the ionic reaction

does indeed occur, one can assume that a similar intramolecular cyclisation would occur in an alternative form of the molecule, which has a polar electronic structure and is sterically more preferable. The synthesis of the previously unknown tetracyclic conjugated π-electron system of cyclohept[*cd*]-*sym*-indacene (CLXXIII),[93] which can be regarded as an isomer of cyclohepta[*a*]phenalene,[94] was undertaken as an initial test of this hypothesis:



(CLXXIII) (CLXXII) (CLXXIV)

Both NMR data and LCAO-MO calculations for the carbon skeleton of compound (CLXXIII) suggest that the polar structure (CLXXIIIa), similar to that of sesquifulvalene, predominates in the true state of compound (CLXXIII):



(CLXXIIIa)

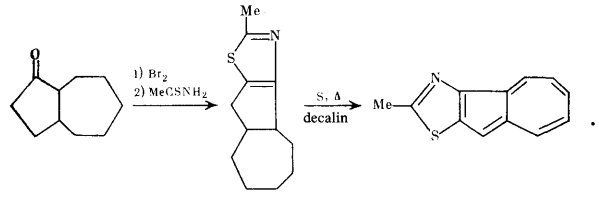
The structure of the alternative product (CLXXIV) has not been finally established although the authors ascribe to it the structure indicated on the basis of mass-spectrometric data and the positions of the absorption bands in the electronic spectrum. Compounds (CLXXIII) and (CLXXIV) are unstable.

The chemistry of such azulene-like polycyclic systems, which sometimes do not obey the Hückel rule, is a matter for the future and is of great theoretical interest from the standpoint of synthesis, stability, and chemical and physicochemical properties.

III. STRUCTURES WITH CONDENSED NITROGEN-, SULPHUR-, AND OXYGEN-CONTAINING HETEROCYCLES

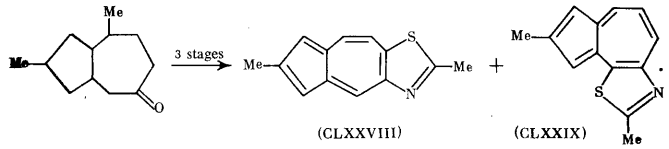
1. Total Syntheses Involving Dehydrogenation

As already mentioned, we include among the total syntheses methods whereby polycyclic azulenes are obtained employing starting materials which are not azulene derivatives and which usually involve a dehydrogenation stage. For example, the bromination of bicyclo[5.3.0]-1-decanone (CLXXV) and subsequent treatment of the resulting α-bromoketone with thioacetamide lead to the thiazole derivative (CLXXVI), which is dehydrogenated by sulphur to 2′-methylthiazole[4′,5′ : 1,2]-azulene (CLXXVII),[95] whose ultraviolet spectrum is close to that of 1,2-benzazulene:



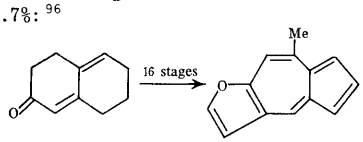
(CLXXV) (CLXXVI) (CLXXVII)

Similarly, 2,8-dimethylbicyclo[5,3,0]-5-decanone gives rise to the two isomeric compounds (CLXXVIII) and (CLXXIX) in proportions of 7 : 1 respectively:



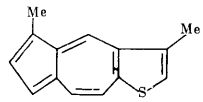
(CLXXVIII) (CLXXIX)

The synthesis of 3,8-dimethylazuleno[6,5-*b*]furan (CLXXX) from naphthalene derivatives has been patented. The synthesis consists of 16 stages and the overall yield of compound (CLXXX) is 0.7%:[96]



(CLXXX)

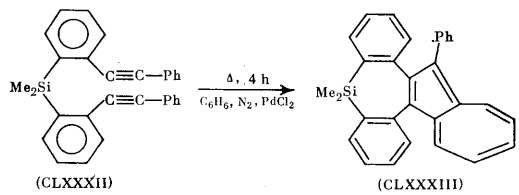
When the sequiterpene fraction of camphor oil is dehydrogenated with sulphur, a small amount of 3,5,8-trimethylazuleno[6,5-*b*]thiophen (CLXXXI) is formed together with *S*-guaiazulene and vetivazulene[97]:



(CLXXXI)

2. Syntheses Based on Acetylenic Derivatives and Other Methods

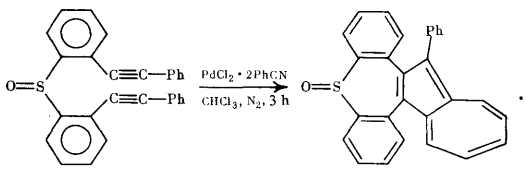
The catalytic rearrangement of the silicon-containing acetylenic hydrocarbons (CLXXXII), leading to a 30% yield of 5,5-dimethyl-10-phenylazuleno[1,2-*d*]dibenzo[*bf*]silepin (CLXXXIII) has been reported[98]:



(CLXXXII) (CLXXXIII)

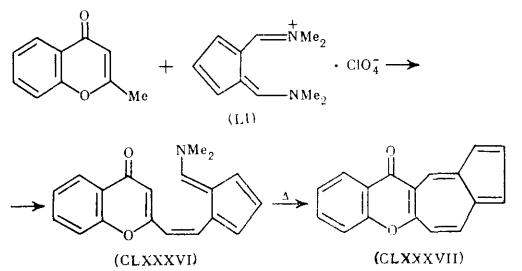
Later the same workers[99] published a synthesis of 5-oxo-10-phenylazuleno[1,2-*d*]dibenzo[*bf*]thiepin (CLXXXV), carried

out by treating the diyne (CLXXXIV) with the complex catalyst $PdCl_2.2PhCN$:



(CLXXXIV) (CLXXXV)

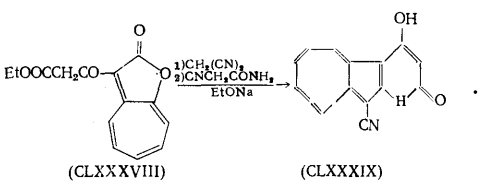
2-Methylchromone has been condensed[50] with a heptamethinium salt (LI) in the presence of sodium methoxide in quinoline, the enamine (CLXXXVI) formed splitting off dimethylamine on heating and giving a 43% yield of azuleno-[6,5-*b*]chromen-12-one (CLXXXVII):



(LI)

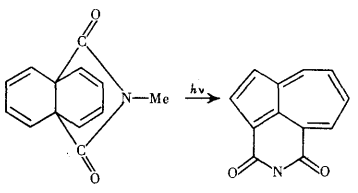
(CLXXXVI) (CLXXXVII)

Japanese workers[100] obtained 10-cyano-4-hydroxyazuleno-[1,2-*e*]-2-pyridone (CLXXXIX) from the 2*H*-cyclohepta[*b*]-2-furanone derivative (CLXXXVIII) by multistage condensation with malononitrile and cyanoacetamide:



(CLXXXVIII) (CLXXXIX)

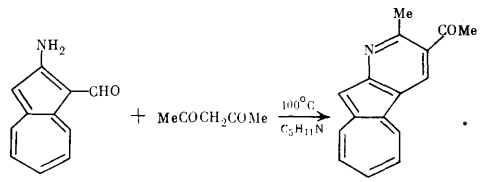
When propellane (CXC) is irradiated with ultraviolet light, the *N*-methylimide of azulene-1,8-dicarboxylic acid (CXCI) is formed in 4% yield together with a series of other compounds[101]. This reaction is of interest because in this case one of the carbocyclic rings contracts with the simultaneous expansion of the neighbouring heterocyclic and cyclohexadiene rings:



(CXC) (CXCI)

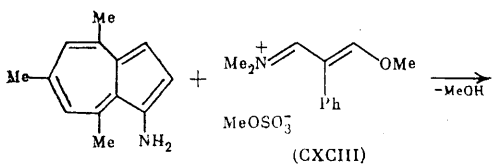
3. Azulene Derivatives in the Synthesis of Heterocyclic Azulenoid Systems

The application of azulenes with functional groups in the synthesis of polycyclic azulenoid systems, including nitrogen- and sulphur-containing heterocycles, constitutes at the present time the most universal method, which has led to the preparation of an extremely large number of a wide variety of compounds of this series. The presence of a free or an acyl-substituted amino-group in the azulene nucleus made it possible to obtain azulenopyridines of various structures as well as other nitrogen-containing derivatives. Thus the condensation of 2-amino-1-formylazulene with acetylacetone in the presence of piperidine makes it possible to obtain 3-acetyl-2-methylazuleno[2,1-*b*]pyridine (CXCII):[102]

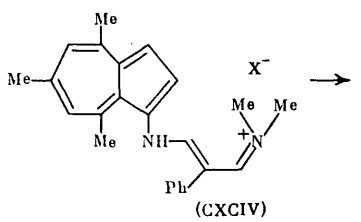


(CXCII)

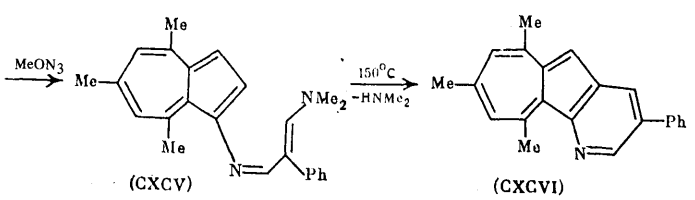
Another isomeric azulenopyridine derivative has been synthesised[57] by the condensation of 1-amino-4,6,8-trimethylazulene with the trimethinium salt (CXCIII). The azulenyltrimethinium salt (CXCIV) is formed initially and is then isolated in the form of the sparingly soluble perchlorate. On reaction with sodium methoxide, the salt splits off perchloric acid and is converted into the amidine (CXCV), which splits off dimethylamine at a temperature as low as 150 °C with formation of 6,8,10-trimethyl-3-phenylazuleno[1,2-*b*]pyridine (CXCVI):



(CXCIII)



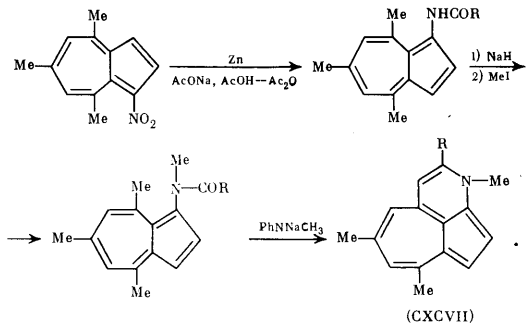
(CXCIV)



(CXCV) (CXCVI)

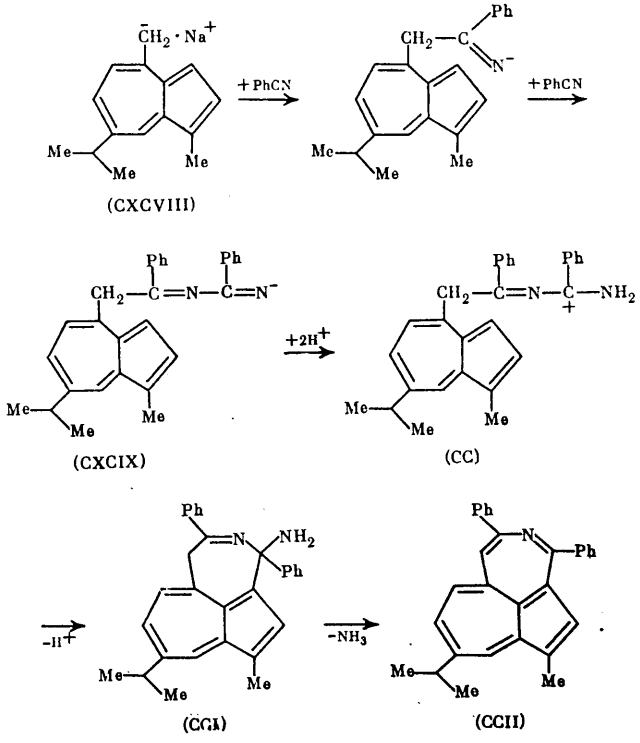
The mobility of the hydrogen atoms of the methyl groups in TMA can be used to synthesise a new pyridine ring condensed along the *cd* faces of the azulene nucleus. An example of this synthesis is provided by the preparation of 1,2,5,7-tetramethyl-1*H*-cyclohepta[*d*,*e*]-1-pyrindine or 1,5,7-trimethyl-2-phenyl-1*H*-cyclohepta[*d*,*e*]-1-pyrindine

(CXCVII) in accordance with the following scheme[103]:

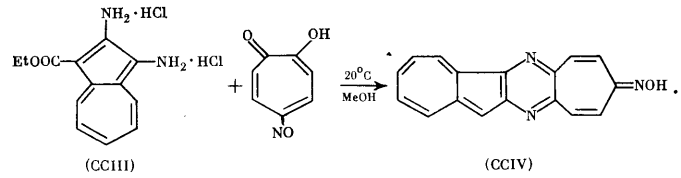


(CXCVII)

The sodio-derivative of guaiazulene (CXCVIII) condenses with benzonitrile to form the amidinium ion (CXCIX) (as the double accretion product), which forms in an acid medium the conjugated carbonium cation (CC), the latter cyclising intramolecularly to the unstable intermediate ketimine (CCI). As a result of the elimination of ammonia from the enamine (the ketimine–enamine tautomerism), the stable aromatic system of 6-isopropyl-8-methyl-2,10-diphenylazuleno[8,9,1-*de*]-azepine (CCII) is formed[104]:

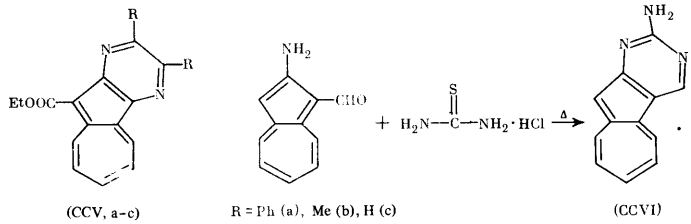


Heterocyclic azulene-containing systems with two nitrogen atoms in the heterocycle can be readily obtained from 1,2-diaminoazulenes. Thus the synthesis of a series of polycyclic derivatives based on 1,2-diamino-3-ethoxycarbonylazulene has been described[105]. When compound (CCIII) was condensed with 5-nitroso-tropolone in methanol, the tetracyclic tropone oxime (CCIV), containing the pyrazine ring in the system, was obtained:



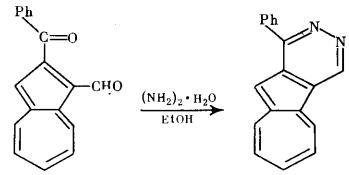
(CCIII) (CCIV)

The condensation of the same diamine with α-dicarbonyl compounds (benzil, diacetyl, or the bisulphite derivative of glyoxal) leads to the corresponding azulenopyrazines (CCV, a–c). The same workers described also the synthesis of the aminoazulenopyrimidine (CCVI):

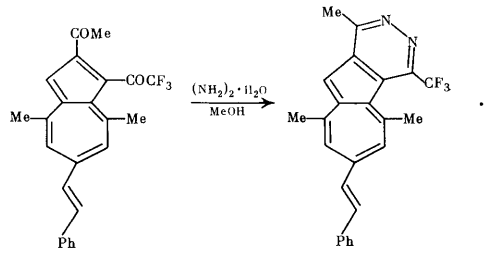


(CCV, a-c) R = Ph (a), Me (b), H (c) (CCVI)

In the presence of two carbonyl groups in the azulene ring, for example the ketone and aldehyde groups, condensation with hydrazine leads to the formation of the azulenopyridazine derivatives (CCVII) [59] and (CCVIII): [39]

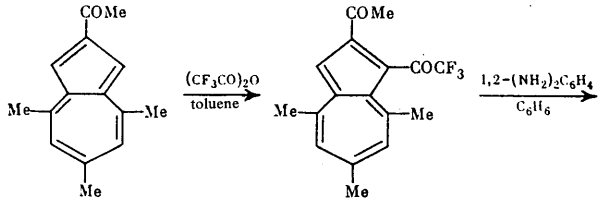


(CCVII)

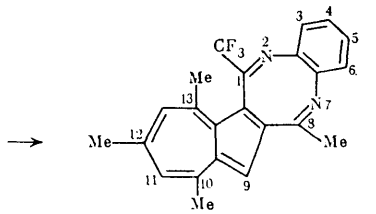


(CCVIII)

Trifluoroacylation of 2-acetyl-TMA (CCIX), obtained by the thermal reaction of TMA with malonic acid[106], results in the formation of the 1,2-diketone (CCX), whose condensation with *o*-phenylenediamine yields the new tetracyclic system 1-trifluoromethyl-8,10,12-14-tetramethylbenzo[*b*]azuleno-[2,1-*f*]-2,7-diazacyclo-octa-2′,4′,6′,8′-tetraene (CCXI): [39]

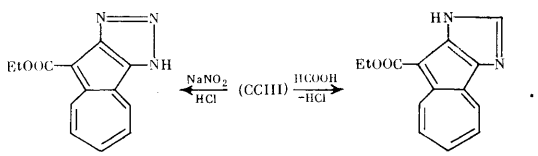


(CCIX) (CCX)



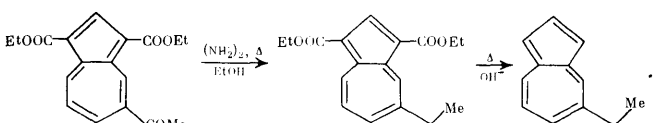
(CCXI)

Derivatives of 1,2-diaminoazulene of type (CCIII) can be readily converted into tricyclic systems containing pyrazole or triazole rings, by their condensation with formic acid or by the diazotisation of one of the amino-groups respectively[105]. The 3-ethoxycarbonyl derivatives of azuleno[1,2-*d*]imidazole (CCXII) and azuleno[1,2-*d*]triazole (CCXIII) have been obtained in this way:



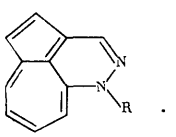
(CCXIII) (CCXII)

The presence of the electron-accepting ketone group in the seven-membered ring, particularly in azulenes in which the electron density is already reduced, such as, for example, 1,3-diethoxycarbonylazulene, the sensitivity of the seven-membered ring to nucleophilic addition increases so much that it permits the synthesis of a pyrazole system, condensed via one of the faces of the seven-membered ring, by the usual condensation of the corresponding derivatives with hydrazine. 5,7-Diethoxycarbonyl-3-methylazuleno[5,6-*d*]pyrazole was obtained in this way[107], the reaction evidently involving the intermediate formation of a hydrazone and its oxidation to the final product. At an elevated temperature the alkaline hydrolysis and decarboxylation of compound (CCXV) lead to 3-methylazuleno[5,6-*d*]pyrazole[108]:



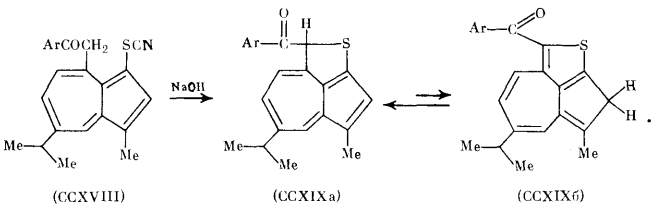
(CCXIV) (CCXV) (CCXVI)

Yet another new polycyclic structure, namely 1*H*-azuleno-[3,10,4-*de*]-1-R-pyridazine (CCXVII) has been obtained[109]:



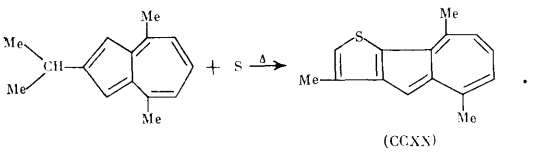
(CCXVII)

Several polycyclic systems incorporating condensed sulphur-containing heterocycles have been obtained from various azulene derivatives with functional groups. Thus the azulenocyclothiophen derivatives (CCXIX) is formed from the thiocyanatoazulenyl ketone (CCXVIII) and it has been established that the azulenodihydrothiophen tautomer (CCXIXa) is thermodynamically more favourable than the heptafulvenothiophen (CCXIXb):[110]



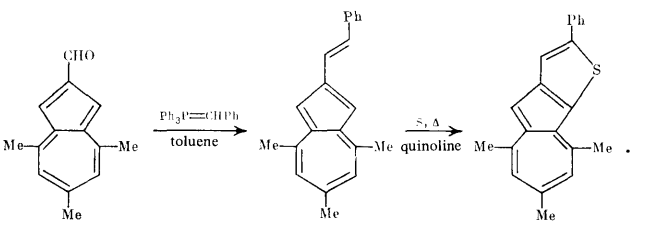
(CCXVIII) (CCXIXa) (CCXIXb)

The high electron density in the 1- (or 3-) position in various alkylazulenes makes it possible to arrive at the azulenothiophen system as a result of the usual dehydrogenation with elemental sulphur. For example, when vetivazulene is heated with sulphur at 200 °C for 4 h in nitrogen, 3,5,9-trimethylazuleno[1,2-*b*]thiophen (CCXX) is formed in 18% yield[111]:



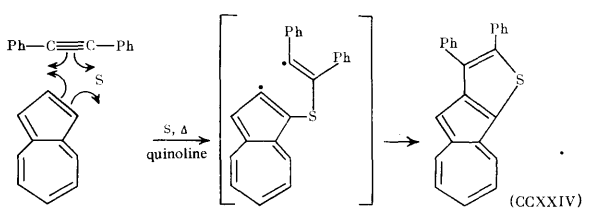
(CCXX)

After it had been established that 1-formyl-TMA undergoes thermal isomerisation to the 2-formyl isomer (CCXXI),[112] a thienoazulene derivative was synthesised via 2-styryl-TMA (CCXXII):[39]



(CCXXI) (CCXXII) (CCXXIII), (22%)

When azulene is heated with sulphur in the presence of diphenylacetylene, dehydrogenation takes place with condensation of the reactants to 2,3-diphenylazuleno[1,2-*b*]-thiophen (CCXXIV) in 8% yield[39]:

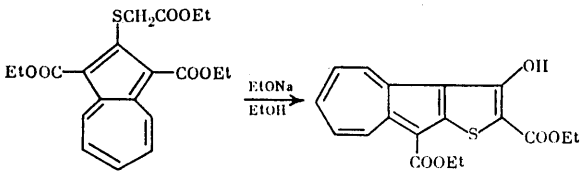


(CCXXIV)

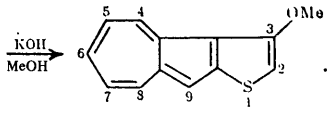
The authors explained the unusual condensation of azulene with diphenylacetylene by the formation of a five-centre intermediate state which is converted into a biradical, the latter recombining to the stable thienoazuleno system. The reaction is accompanied by the formation of a considerable amount of tetraphenylthiophen.

The presence of the thioglycolic residue in the 2-position in azulene made it possible to achieve the cyclisation of the ester (CCXXV) under the conditions of the Dieckmann reaction with its transformation via the hydroxyester (CCXXVI)

into 3-methoxyazuleno[2,1-*b*]thiophen (CCXXVII):[113]

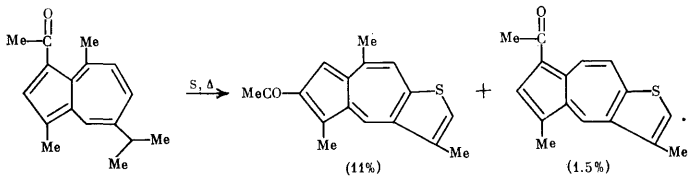


(CCXXV) (CCXXVI)



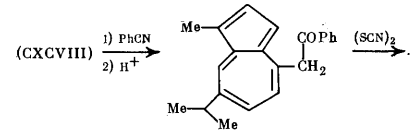
(CCXXVII)

The synthesis of 5- and 7-isopropylazuleno[2,1-*b*]thiophens has been described[114] and the cationic substitution of such systems has been investigated[115]. The thermal reaction of 3-acetylguaiazulene with sulphur, leading to the formation, apart from the 2-acetyl derivative, of azulenothiophens in which the thiophen ring is annellated along the *f* face of azulene [at the C(5) and C(6) atoms] is known[116]:

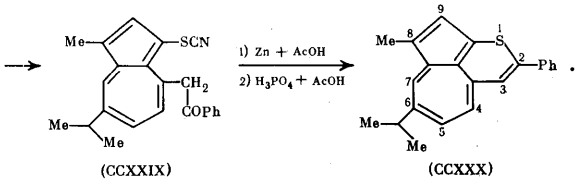


(11%) (1.5%)

The mobility of the hydrogen atoms in the 4-methyl group of guaiazulene makes it possible to obtain the sodio-derivative (CXCVIII), which condenses with benzonitrile to 7-isopropyl-1-methyl-4-phenacylazulene (CCXXVIII). The reaction of the latter with free thiocyanogen, the reduction of the thiocyanate (CCXXIX) with zinc in acetic acid, and intramolecular cyclisation of the intermediate mercapto-derivative, evidently with the enolic form of the phenacyl group, lead to a new azulenoid system—6-isopropyl-8-methyl-2-phenylazuleno[1,9,8-*bc*]thiapyran (CCXXX):[117]



(CCXXVIII)



(CCXXIX) (CCXXX)

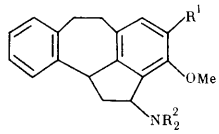
Later a similar system was obtained from TMA.[104] Agreement between the theoretically predicted and experimentally observed mode of electrophilic substitution has been demonstrated for the condensed heterocyclic system (CCXXX).

Thus the Mannich reaction takes place exclusively in the 9-position (yield 79%); the Vilsmeier–Haack formylation of compound (CCXXX) gives rise to the 9-formyl derivative (39%) and the 4-formyl derivative (30%).[118]

The examples of the synthesis of polycyclic azulenes presented above do not exhaust all the possibilities of obtaining more highly condensed and complex carbocyclic and heterocyclic derivatives of this class. The employment of polyfunctional substituted azulenes with polyene residues and heterochain substituents is particularly promising in this field[39].

IV. PHYSIOLOGICAL PROPERTIES OF POLYCYCLIC AZULENES

Until recently, there has been virtually no information in the literature about the physiological activity of polycyclic azulene hydrocarbons and their derivatives, which can probably be accounted for by the fact that many representatives of this class are difficult to synthesise and have been obtained comparatively recently. It is only known that 3-acetyl-2-methylazuleno[2,1-*b*]pyridine as well as 5,7-diethoxycarbonyl-3-methylpyrazolo[4,3-*f*]azulene have been patented as preparations with antipyretic and anti-inflammatory activities[102,108]. 3-Methylpyrazolo[4,3-*f*]azulene has sedative and analgesic properties[108]. Azulene derivatives with analgesic, antidepressant, sedative, and hypotensive properties have been obtained [these derivatives should be more appropriately assigned to the class of hydrogenated azulenylamines of type (CCXXXI)]:[119]



(CCXXXI) R^1 = OH, OMe; R^2 = H, Me .

Certain other derivatives of the series of compounds (CCXXXI) possess similar properties[120]. *l*-3,5β,8β-Trimethyl-4,5,5aα,6,7,8,8aα,9-octahydroazuleno[5,6-*b*]furan[121], which possesses sedative, analgesic, and anticough properties, is known among hydrogenated azulene derivatives. A strong carcinogenic activity is attributed to aceazulenophenalene[49] and a group of other polycyclic azulenes[122]. The azulenofuran (CLXXX) has been patented as a preparation which is effective in the treatment of cancer and stomach ulcers[96].

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