Accounts

Chemistry of Azulenequinones and Their Analogues

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Azulenequinones have been attracting great interest in recent years. After a brief introduction concerning an earlier study of azulenequinones we review recently developed areas of azulenequinone chemistry, which became possible by the discovery of a facile one-pot synthesis of azulenequinones, or their bromo derivatives, by means of the bromine oxidation of various azulene derivatives in an aqueous solvent. Various functionalized, and some annulated, azulenes are used as substrates to determine the scope and limitations of this method. The bromoazulenequinones can be used as synthons, from which various azulenequinones can be derived by nucleophilic displacement. In a hope to encourage other chemists to develop new azulenequinone chemistry, we herein describe the process of the discovery, starting from the original motivation. In addition, we touch on remarkable and mysterious products whose structures remain undetermined and our speculation concerning their reaction paths. Some physical and chemical properties of azulenequinones, together with those of azulenequinone methides and diazoazulenequinones, are also described. This is the first complete review of the field of newly developing azulenequinones.

As is well known, quinones are among the oldest known compounds and involve one of the most interesting areas in organic chemistry.[1,2] Since centuries ago, they have had many important applications, such as dyestuffs as well as antibiotic, antifungal, and antitumor medicines. However, almost all of them belonged to benzenoid compounds.[1a,b]

In 1963, Hafner et al.[3] started an extensive study of fulvene chemistry, and synthesized some 2-methylene-6(2*H*)-azulenone derivatives **3** (R,R′ = Me, Ph, *N*-piperidino), which correspond to 2,6-azulenequinone-2-methides, by a base-catalyzed condensation of diethyl 3-oxopentanedioate (**1**) and 6-(*N*,*N*-disubstituted)fulvene-3,4-dicarbaldehyde (**2**) (Scheme 1).

On the other hand, Marsili and Isola[4a] obtained polycondensed 1,6-azulenequinone (**4**) and Ried and Ehret[4b] synthesized 2,6-azulenequinone derivatives (**5**), as shown in Scheme 2.

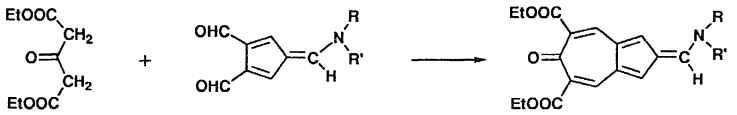
Around the same period, Nozoe, Asao, and Ando[5a—c] obtained 2-diazo-6(2*H*)-azulenones (2,6-azulenequinone 2-diazides) by the diazotization of 2-amino-6-bromoazulenes (**6a,b**). Based on infrared spectral data they thought that **7a** (R = COOEt) and **7b** (R = CN) made a considerable contribution to the dipolar form (**A′**), and thus called the compounds "diazoazulenoquinones" or "diazoazulenolates".[5a,b] They also obtained 2-diazo-4(2*H*)-azulenone (**9a,b**) from **8a,b** by a similar method[5a—c] (Scheme 3).

A little later, Morita, Takase, and co-workers synthesized several 1,2-, 1,5-, and 1,7-azulenequinone derivatives from polysubstituted azulenes **12** (R^1, R^3 = COOEt, CN, etc.; R^2 = OH or NH_2),[1d] which were easily obtainable by the Nozoe azulene synthesis[1d,6] from reactive troponoids **10** (having a good leaving group, such as OMe, Cl, and OTs at C-2) and various active methylene compounds (AMC) via cyclohepta[*b*]furan-2-ones (**11a**: X = O) or -imines (**11b**: X = NH) (Scheme 4).

Meanwhile, Matsubara, Yamamoto, Nozoe, and co-workers started an extensive study in 1980 on the autoxidation of naturally occurring guaiazulene (**13**) and synthetic 4,6,8-trimethylazulene (**14**), and obtained a small amount of guaiazulenequinone (**15**) and 4,6,8-trimethyl-1,5- (**16**) and -1,7-azulenequinones (**17**). The yields of the azulenequinones were greatly improved by using peracetic acid as an oxidant[1e] (Scheme 5).

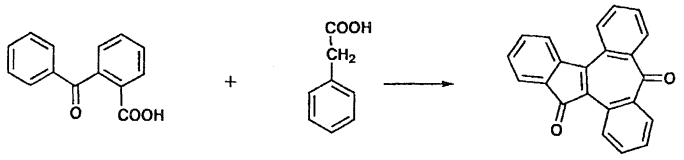
Almost at the same time, Scott, Houk, Fukunaga, Hafner, and co-workers published a joint paper[2] describing sixteen possible structures of azulenequinones. They also predicted the physical properties of the azulenequinones in terms of the UV spectra, magnetic susceptibility, redox potential, stability, etc. based on a theoretical calculation. The calculation suggested that only 1,2-, 1,5-, and 1,7-azulenequinones should be stable. They stressed that the azulenequinones would be very promising candidates for antibacterial,

#Deceased in April 4, 1996.



1 2 3

Scheme 1.



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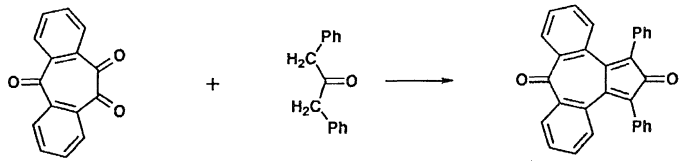

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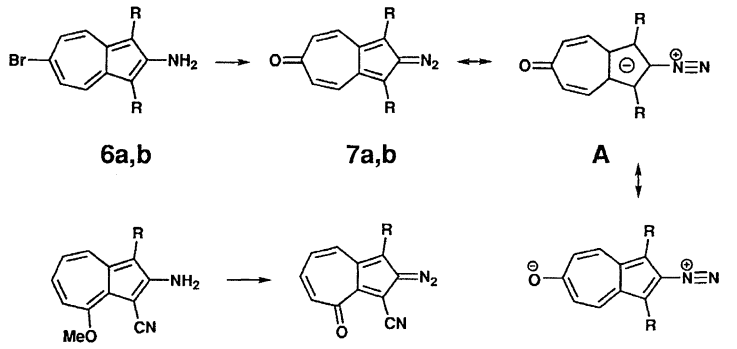
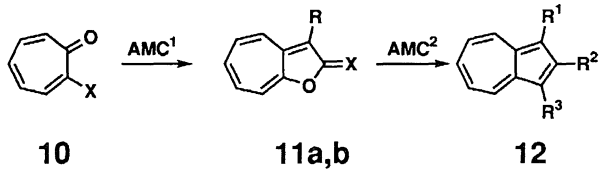
Scheme 2.



6a,b 7a,b A

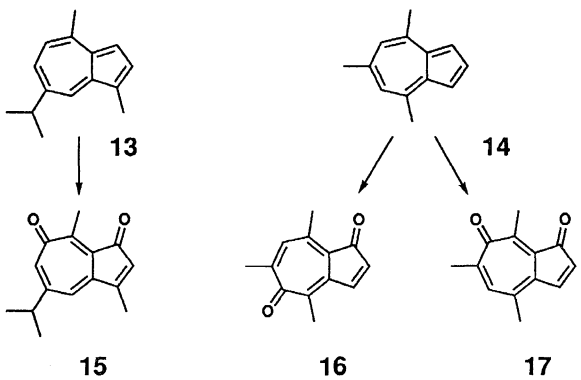
8a,b 9a,b A'

Scheme 3.



10 11a,b 12

Scheme 4.



13 14

15 16 17

Scheme 5.

antifungal, and antitumor examination, and might play an important role in photosynthesis as well as in the respiratory electron transport chain and solid state electroconductivity. Indeed, in 1984 they succeeded in the first synthesis of highly reactive 1,4- and 1,6-azulenequinones as Diels–Alder adducts, and isolated 1,5- and 1,7-azulenequinones as stable crystals.[2] These experimental findings drew increasing attention of chemists around the world to azulenequinones.

On the other hand, in 1985 Nozoe, Ishikawa, Shindo, and Wakabayashi started a systematic study on the bromination of various azulenes, which led to the discovery of a very facile one-pot synthesis of 1,5- and 1,7-azulenequinones. We herein review important aspects of these recent studies concerning azulenequinone chemistry, and anticipate not only further developments in its fundamental chemistry, but also new applications. Although an extensive and excellent review[1c] of azulenequinones was published by Scott in Patai's monograph[1a] in 1988, it referred only to the studies of Morita et al. and Scott et al. The present account is therefore aimed at covering more extensive aspects of azulenequinones and related compounds while being the first complete review.

Synthesis of Azulenequinones and Related Compounds

A. From Polysubstituted Azulenes via Azulenediols. 2,6-Azulenequinone. The aforementioned original one-pot synthetic procedures[6a—c] for the polysubstituted azulenes (**12**) from troponoid **10** or **11a,b** were further developed. Various functional groups originally introduced by the Nozoe azulene synthesis can be either eliminated or replaced by other groups, thereby affording a wide variety of polysubstituted azulenes.[1f,6b—f] These azulenes were furnished for azulenequinone synthesis. Morita, Takase, and co-workers thus obtained several azulenequinones from the appropriate azulenes, as shown in the following Schemes (6 to 12).

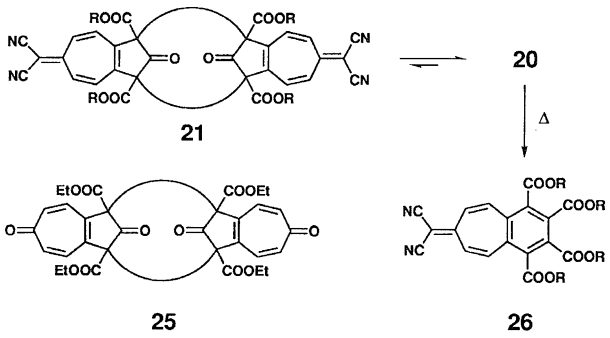
Unlike the free 6-bromoazulen-2-ol (**18a**: R = Me or Et, R′ = H), its *O*-acetate (**18b**: R′ = Ac) easily reacted with sodiomalononitrile to give **19b** (R′ = Ac) in a high yield. Compound **19a** (R′ = H), obtained by the alkaline hydrolysis of **19b**, was dehydrogenated with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) to afford 2,6-azulenequinone-6-methide derivatives (**20**) that were isolable in the dimeric form[7a] (Scheme 6). Similarly, they obtained diethyl 2,6-azulenequinone-1,3-dicarboxylate (**24**), also as the dimeric form, by the dehydrogenation of **23**, which was obtained by the photolysis of 2-diazoazulen-6(2*H*)-one (**7a**) in acetic acid followed by hydrolysis of the 2-OAc group of **22**[7b] (Scheme 7).

Highly reactive 2,6-azulenequinones (**20** and **24**) were isolated only as dimers **21** and **25**, respectively. These dimers are stable at 100 °C, but revert to **19a** (R′ = H) and **22** when treated with a sodium hydrogensulfite solution or zinc in acetic acid. Compound **21** was condensed with acetylenedicarboxylate to give benzoheptafulvene derivative **26**. This experimental evidence shows that dimers **21** and **25** dissociate respectively to monomers **20** and **24** before reduction and cycloaddition[7] (Scheme 8).

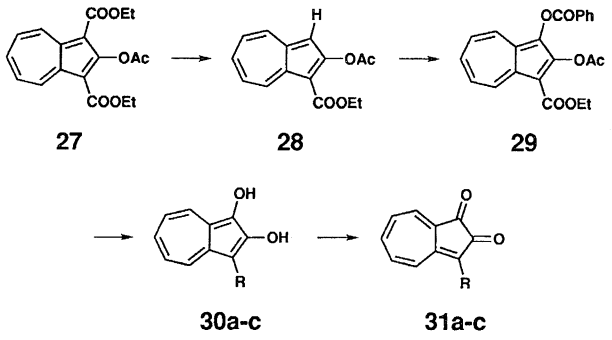
1,2-Azulenequinones. Morita et al.[8] also synthesized parent 1,2-azulenequinone (**31a**: R = H) as the first example of a stable non-annulated azulenequinone. Starting from very easily available diethyl 2-acetoxyazulene-1,3-dicarboxylate (**27**), monodeethoxycarbonylated compound **28** was derived, then benzoyloxylated with benzoyl peroxide in benzene at 80 °C to give compound **29**. Upon a treatment with 100% H_3PO_4 at 90 °C for 50 min **29** underwent hydrolysis of the acetoxy and benzoyloxy groups accompanied by deethoxycarbonylation to yield very unstable 1,2-azulenediol (**30a**: R = H). Compound **30a** was immediately treated with DDQ at room temperature to give 1,2-azulenequinone (**31a**) as green needles. They also obtained 3-ethoxycarbonyl- (**31b**: R = COOEt) and 3-cyano-1,2-azulenequinone (**31c**: R = CN)[8] (Scheme 9).

1,5- and 1,7-Azulenequinones. Then, Morita et al. prepared methyl 1,5- (**35**) and 1,7-azulenequinone-3-carboxylates (**36**),[9] as shown in Scheme 10. Namely, methyl 5-methoxy- (**33a**) and 7-methoxyazulene-1-carboxylates (**33b**), obtained by monodemethoxycarbonylation of diethyl dicarboxylate (**32**), were oxidized with lead tetraacetate in benzene–pyridine–DMSO to give 3-acetoxy compounds **34a** and **34b**, which were further oxidized with cerium(IV) ammonium nitrate to provide methyl 1,5- (**35**) and 1,7-azulenequinone-3-carboxylates (**36**) in 71 and 73% yields, respectively. As predicted by Scott et al.,[2] 1,2-, 1,5-, and 1,7-azulenequinones were stable compounds.

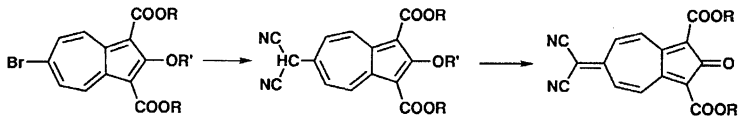
1,6-Azulenequinone. A 1-dimethylaminomethide derivative of 1,6-azulenequinone (**39**) was also prepared by Morita et al., starting from 6-acetoxyazulene (**37**), as shown in Scheme 11. Namely, the reaction of **37** with dimethylformamide-phosphoryl chloride at 0 °C for 30 min afforded 1-formyl derivatives **38a,b** (R = H and Ac) and **39**. On the other hand, a treatment of 6-azulenol with DMF–$POCl_3$ at 0 °C for 30 min, followed by the addition of 40% dimethylamine, afforded **39** in 100% yield. The hydrolysis of **39**



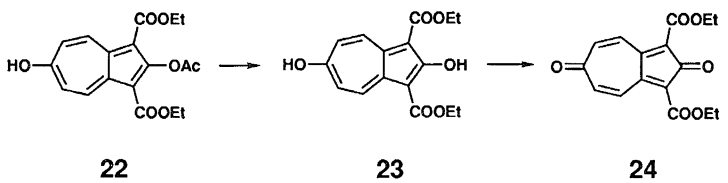
Scheme 8.



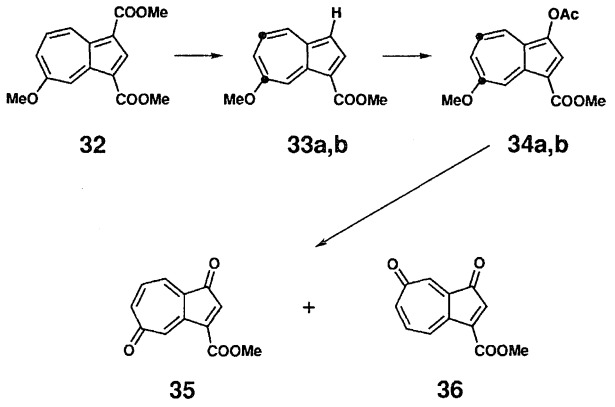
Scheme 9.



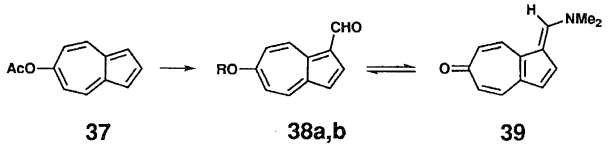
Scheme 6.



Scheme 7.



Scheme 10.



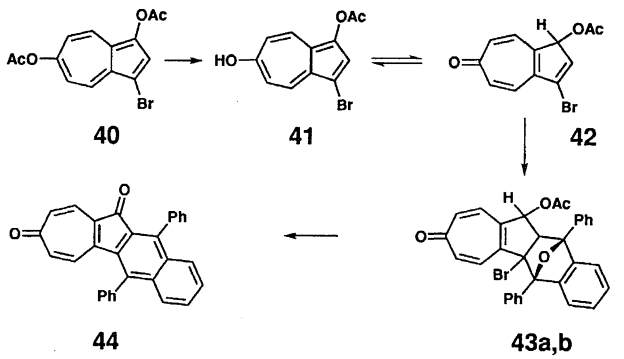
Scheme 11.

with sodium hydroxide in ethanol easily reproduced **38a**.[10a)]

They also synthesized mono-annulated 1,6-azulenequinone derivative (**44**) from 3-bromo-1,6-diacetoxyazulene (**40**), as shown in Scheme 12. Thus, the treatment of **40** with 30% aqueous dimethylamine at room temperature gave **41**, which exists as a solvent-dependent tautomerism between **41** and **42**. A Diels–Alder condensation of the latter (**42**) with 1,3-diphenylisobenzofuran afforded adducts **43a** (and its isomer **43b**), which gave the naphtho-fused 1,6-azulenequinone (**44**) upon a treatment with hydrochloric acid.[10b)]

B. Oxygenation of Azulenes. Autoxidation. In 1984, Nozoe, Matsubara, Yamamoto, and co-workers found minute amounts (1—1.5%) of guaiazulenequinone (**15**), 4,6,8-trimethyl-1,5- (**16**), and -1,7-azulenequinones (**17**) among many autoxidation products derived from guaiazulene (**13**) and 4,6,8-trimethylazulene (**14**) by passing finely bubbled oxygen into a solution of the substrates in DMF at 100 °C.[11a—c)]

The yields of azulenequinones were very much influenced by the reaction conditions. For example, when a hexane solution of the substrate was impregnated into filter paper and allowed to be exposed to air, the isolated yields of guaiazulenequinone (**15**) varied: 3.8% under sun light, 6.7% in a laboratory, and 18.9% in a dark room.[11d)] The oxidation of guaiazulene in DMF in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) at 100 °C gave a 10% yield of **15**.[11e)]



Scheme 12.

Peracid and H_2O_2 Oxidation. Peracetic acid and H_2O_2 oxidations of azulenes are far more simple. For example, Matsubara, Yamamoto, Nozoe, and co-workers[12a,b)] obtained by the peracetic acid oxidation of **13** in hexane at 25 °C (1 h) "biguaiazulenedione" **45** (80%) together with a trace of guaiazulenequinone (**15**) and 5-isopropylidene-3,8-dimethyl-1(5*H*)-azulenone (**48**). The autoxidation of **45** in pyridine at 25 °C provided as high as 46% of guaiazulenequinone (**15**) and 1% of biguaiazulenequinone (**47**). Moreover, the autoxidation of **45** in $CHCl_3$ (or CH_2Cl_2) at 25 °C afforded **48** as a major product (30%). These reactions of **13** were assumed to proceed via a monomeric guaiazulenone radical (**45a**), as shown in Scheme 13.[12d,e)]Later, Asao, Matsubara, Nozoe, and co-workers established the structure of "biguaiazulenediones" to be a mixture of *meso* and the enantiomers (**45**).[12c)] These biguaiazulenediones turned out to be a highly important key intermediate for the various autoxidation products of guaiazulene. The oxidation of 4,6,8-trimethylazulene (**14**) with H_2O_2 in pyridine also afforded azulenequinones (**16** and **17**) (8% each) and 2-azulenylazulenequinones (**49a** and **49b**) (9%), together with various dimeric rearranged products[12f)] (Chart 1).

MnO_2 Oxidation. Very recently, Hansen and co-workers obtained **15**, 7-isopropyl-4-methyl-1,5-azulenequinone (**50a**) and its 1,7-isomer (**50b**) from guaiazulene (**13**) by MnO_2 oxidation[13a)] (Chart 1).

Photo-Oxygenation. Wu, Yang, Nozoe, and co-workers examined the photo-oxygenation of some functionalized azulenes. The reaction products were a mixture of various mono-, bi-, and terazulene derivatives, somewhat similar to the cases of the autoxidation of azulenes.[11)] A very small amount (1—1.5%) of azulenequinones was isolated from other oxidation products. Namely, 2,4-diethoxyazulene (**51**) and 4-dimethylamino-2-ethoxyazulene (**52**) afforded a small amount of the corresponding azulenequinones (**53**—**55**), whereas 2-ethoxyazulene (**56**) did not give any azulenequinone, but afforded some interesting bi- and terazulenone derivatives in good yields[13b)] (Chart 2).

Natural Occurrence. As mentioned later, Li and Scheuer believed guaiazulenequinone (**15**) to be the first natural azulenequinone. During the isolation of the violet pigment linderazulene

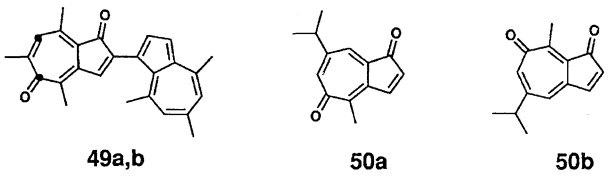


Chart 1.

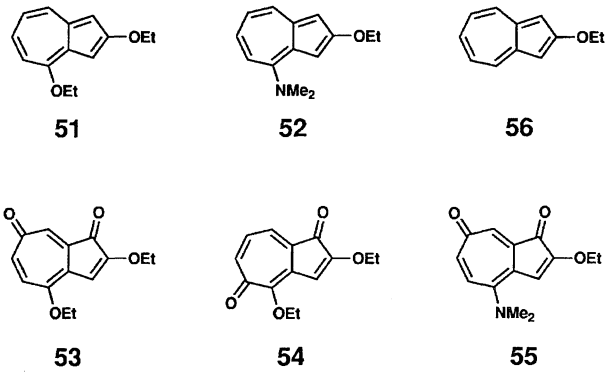
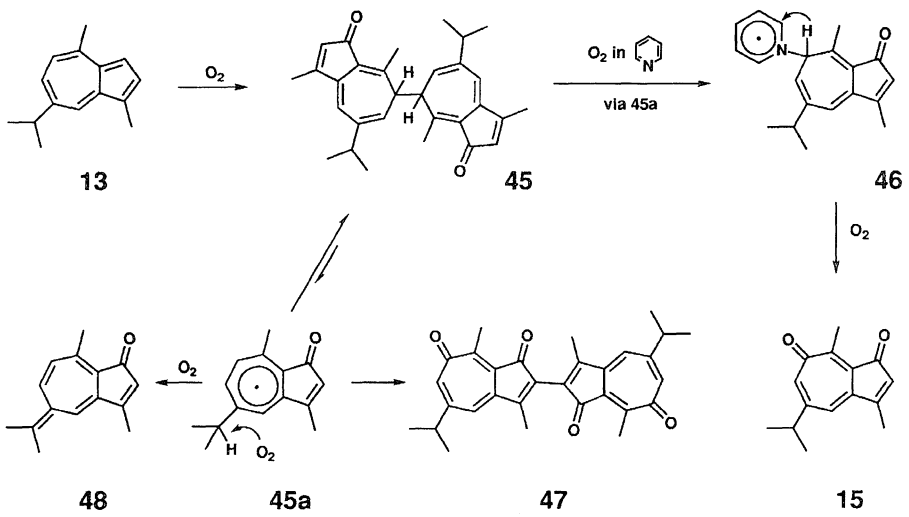


Chart 2.



Scheme 13.

(**57**) from gorgonian *Paramuricea Chamaeleon*. Alpertunga et al. detected a small amount of yellow pigment **58**, which was a photo-oxidation product formed by exposing an ethanol solution of **57** to direct sunlight for six days.[14a] An isomeric extended azulenequinone "malophylidin" (**59**) was isolated from the roots of *Ferula Malacophylla* by Bagirov et al.[14b] (Scheme 14).

Streptomyces echinoruber sp. nov. produces more than five red pigments; the main pigment, "rubrolone A" (**60**), was elucidated to be a complex 1,4-azulenequinone derivative by a chemical reaction and X-ray analysis of its derivative **61**. The structure and absolute stereochemistry of **60** and **61** are shown in Chart 3. The spectra of another pigment (rubrolone B) suggest that it is possibly an isomer of **60**.[14c]

C. From Dihydrocinnamic Acid via Diacetoxyazulenes. Scott et al. have developed a remarkable azulene synthesis without any dehydrogenation steps.[15a,b]

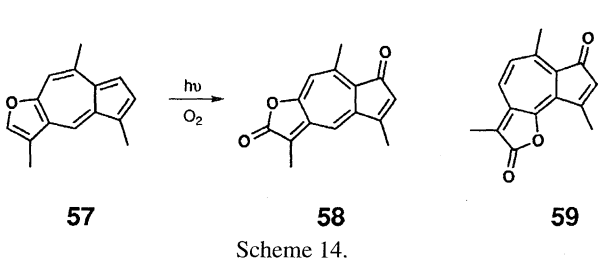
1,4- and 1,6-Azulenequinones. Starting from dihydrocinnamic acid (**62**), diazoketone (**64**) was obtained almost quantitatively via acyl chloride (**63**). Refluxing of **64** with a catalytic amount of copper(I) chloride (or preferably with rhodium(II) acetate)[15c] rapidly afforded bicyclic trienone (**67**) via intramolecular carbene insertion product **65** and ring-enlargement product **66** (in 45—50% yields). The treatment of **67** with P_2O_5 and methanesulfonic acid provided parent azulene,[15b] whereas the oxidation of **67** with CrO_3–pyridine gave a mixture of tropones (**68a** and **68b**), which were respectively transformed into 1,4- (**69a**) and 1,6-diacetoxyazulenes (**69b**) simply by stirring with acetic anhydride and pyridine in hot ethyl acetate. These **69a** and **69b** were treated with methyllithium in THF at −75 °C and then with chlorotrimethylsilane respectively to afford unstable **70a** and **70b**. These compounds were oxidized with pyridinium chlorochromate (PCC) or tetrachloro-*p*-benzoquinone in the presence of cyclopentadiene to give Diels–Alder adducts (**72a** and **72b**) of very unstable 1,4- (**71a**) and 1,6-azulenequinones (**71b**).[15a,16] These **71a** and **71b** were too unstable to be isolated, just as predicted by Scott et al.[2] (Scheme 15).

Alternatively, **69a** was brominated with NBS to give monobromo compound **73**, a treatment of which with methyllithium followed by protonation with acetic acid afforded tropone (**74**). By adding pyridine in the presence of cyclopentadiene, **74** directly produced the Diels–Alder adduct (**72a**)[16a] (Scheme 16).

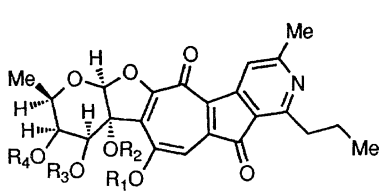
1,5- and 1,7-Azulenequinones. The photo-oxygenation of the aforementioned trienone (**67**) gave a high yield of two isomeric *endo*-peroxides (**75a,b**), both of which were then treated with acetic anhydride and pyridine to afford 1,5- and 1,8-diacetoxyazulenes (**76a,b**) from **75a**, and 1,7-diacetoxyazulene (**76c**) from **75b**. Those **76a** and **76c** led to stable 1,5- and 1,7-azulenequinones (**77** and **78**) respectively in the absence of cyclopentadiene by the aforementioned method[16b] (Scheme 17).

The direct oxygenation of azulene (**79**) with benzoyl peroxide, followed by Friedel–Crafts alkylation with *t*-butyl bromide, yielded 1,3-disubstituted azulene (**81**) via **80**. Chromium trioxide oxidation of **81** in aqueous acetic acid afforded a mixture of 3-*t*-butyl-1,5- and -1,7-azulenequinones (**82a** and **82b**)[15c] (Scheme 18).

D. Bromine Oxidation of Azulenes in Aqueous Solvents. Motivation. In 1984, Li and Scheuer isolated from polyps of Hawaiian deep-sea gorgonian[17] various pigments (guaiazulene (**13**), lactarazulene (**83**), two "one-carbon transferred" compounds **84** and **85**,[11d] and guaiazulenequinone (**15**)), about which Nozoe and co-workers had just published.[11a] Besides them, there were three haloazulenes: 3-chloro- (**86**), 3-bromo- (**87**), and chiral 14-bromoguaiazulene (ehuazulene) (**88**). Scheuer also described that all of these haloazulenes were unstable (Chart 4).

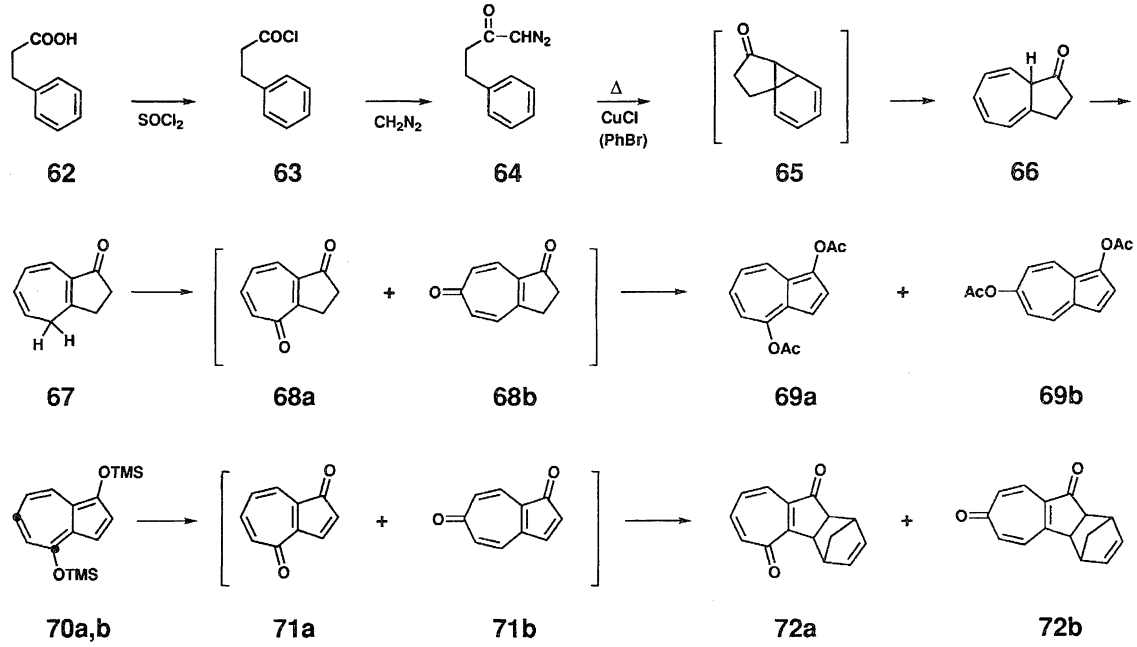


Scheme 14.

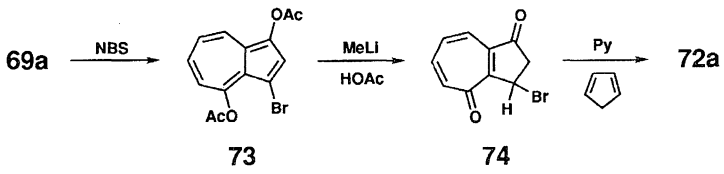


60 (Rubrolone A): R_1=R_2=R_3=R_4=H
61 : R_1=Me, R_2=o-BrC_6H_4CO, R_3,R_4=$CHMe_2$

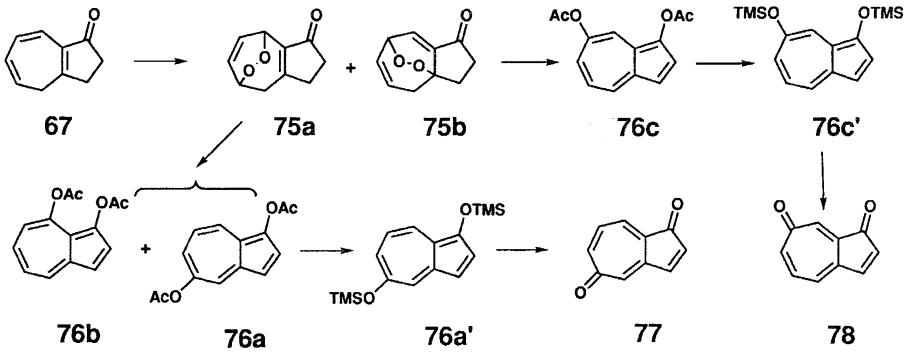
Chart 3.



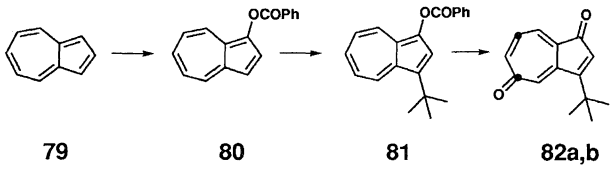
Scheme 15.



Scheme 16.



Scheme 17.



Scheme 18.

Being interested in the discovery by Li and Scheuer, Nozoe started a study concerning the bromination of guaiazulene and other azulene derivatives with Ishikawa, Shindo, and Wakabayashi from the standpoint of fundamental chemistry.

Guaiazulene and NBS in Benzene or Hexane. Upon a treatment with equimolar amount of NBS in benzene at room temperature, guaiazulene **13** surprisingly gave more than 10 products (**88**—**96**); noteworthily, all of those products (except for **90**) had no bromine atom at C-3.[18a] On the other hand, when **13** was treated with NBS in hexane, 3-bromoguaiazulene (**87**) was obtained quantitatively, as expected. However, as shown in Scheme 19,[18a,b] pure **87** in benzene changed within several hours, and gave the same products (**88**—**96**) besides **13** as in the case of the reaction of **13** with NBS in benzene. After having carefully studied the order of the bromine-shift of **87** in benzene by time-dependent HPLC, they postulated the order of the shifts. From experimental evidence that **87** gave two types of coupling products (**95** and **96**) in benzene, and that those Br-shifts shown in Scheme 19 did not occur in the presence of a proton or radical scavenger, they presumed that the Br-shifts proceeded via intra- and intermolecular radical pathways.[18b]

Guaiazulene and NBS in Methanol. In contrast to the aforementioned NBS bromination of **13** in benzene, the reaction of **13** with NBS in methanol produced bromine-free dimers (**95** and its 3,2′-isomers), trimers and oligomers, together with a small portion

of methoxylated products.[18b,c]

Bromination of Synthetic Azulenes with NBS. Then, Nozoe et al. undertook a systematic study of bromination reactions of a wide range of azulenes. For example, the reaction of methyl 7-isopropylazulene-1-carboxylate (**97**) with NBS in benzene at room temperature gave a 3-bromo derivative **98** quantitatively, whereas at 60 °C with a large excess of NBS **103** was produced, presumably via the isopropyl side-chain-brominated and dehydrobrominated products (**99**—**102**), as in the case of the bromination of cumene at higher temperatures[19] (Scheme 20). However, no bromine migra-

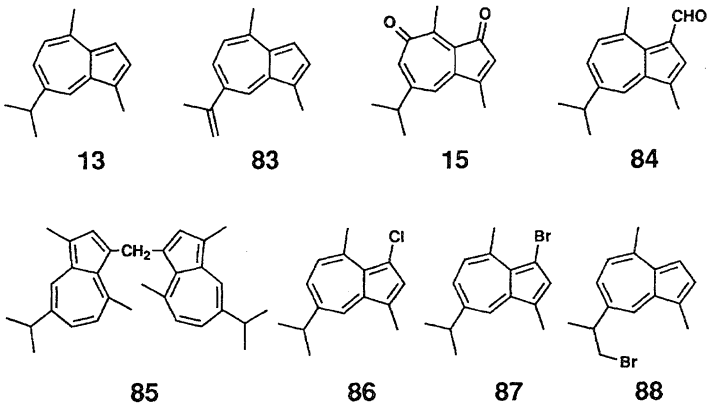
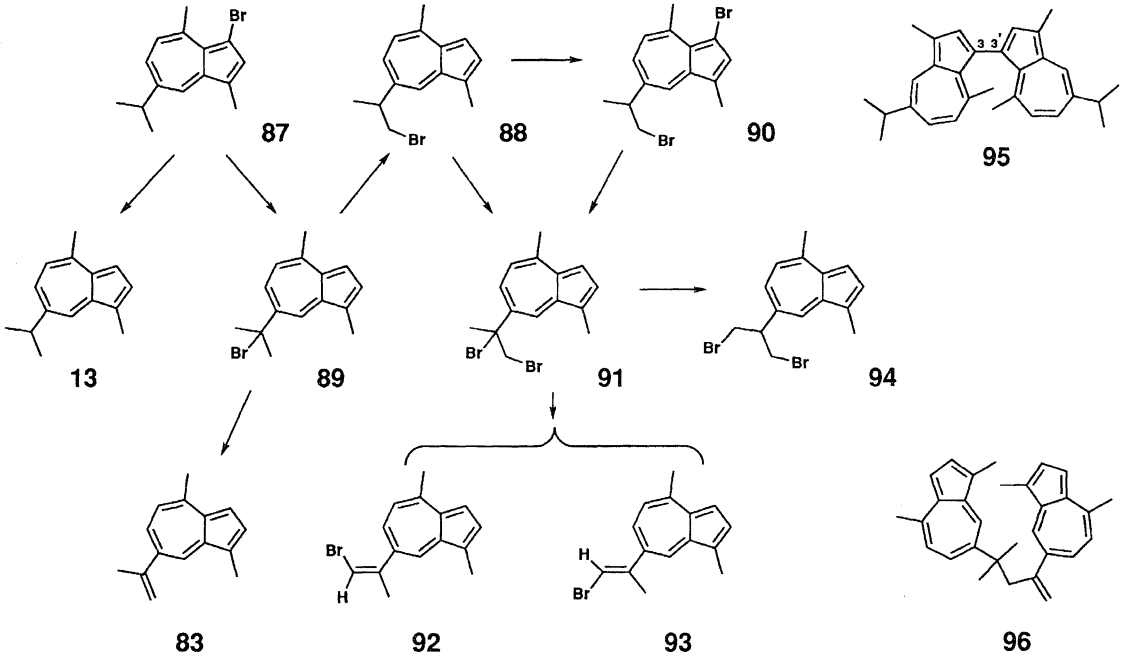
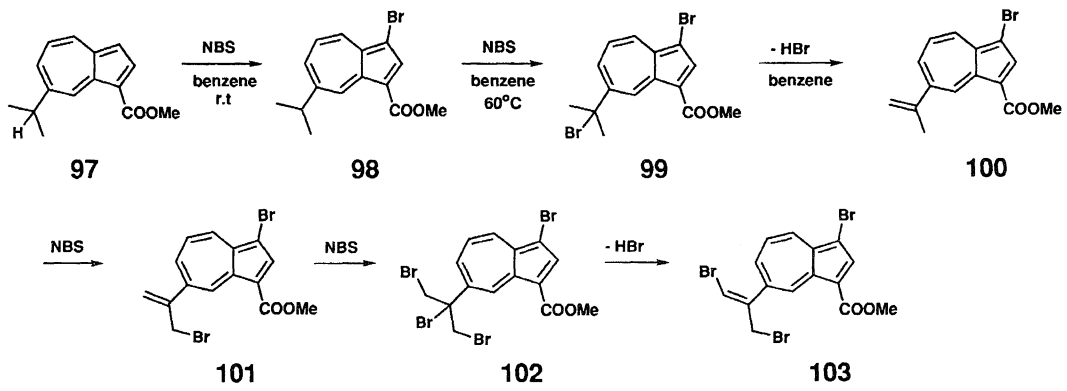


Chart 4.



Scheme 19.



Scheme 20.

tion in benzene was observed among these compounds.

4,6,8-Trimethylazulene (**14**) almost quantitatively gave 1,3-dibromo derivative (**104**) upon a treatment with 2 molar amounts of NBS in benzene.[20a,b] Compound **104** is completely stable in benzene, thus eliminating the possible reasoning of a steric repulsion between the bromine atom and the methyl group at the peri position for the facile bromine migration in benzene observed in the case of **13** and some of its derivatives.[20b] Chart 5 shows the oxidation potentials of **14**, **104**, **13**, and 3-methylguaiazulene (**105**).[20c] It is noted that because of such a low oxidation potential a hexane solution of **105** sprayed on filter paper was instantly oxidized to give variously colored products[20b] (Chart 5).

Thus, the facile bromine shifts of **87** and related compounds **88**—**94** in benzene have been attributed to the significantly low values of their oxidation potentials,[20d] which enable Br^+ of π-complex **106** to take up one electron from the very reactive 10π azulenic system to form a radical cation **107** via the π-complex **106** and a bromine radical $Br^{\bullet}$.[20b] The latter $Br^{\bullet}$ radical, carried by the 6π electron cloud of solvent benzene **108**, then attacks other positions of the substrates intra- or inter-molecularly.[20b] Possible pathways are shown in Scheme 21; benzene containing an absorbed water cluster is presumed to serve as an initial proton source for the conversion of **87** to **106**.

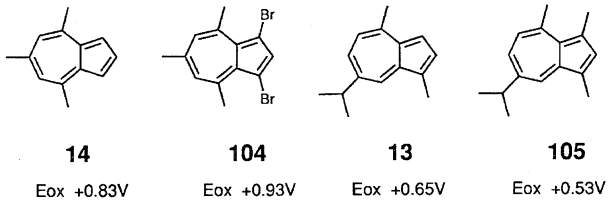


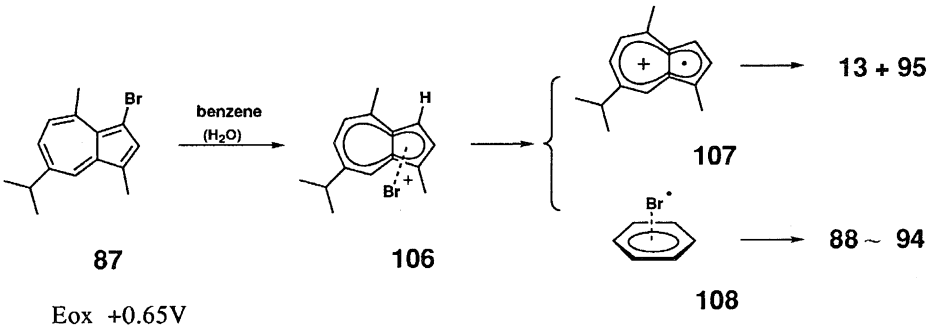
Chart 5.

Bromination of Azulenes in Hexane. Then, Nozoe, Ishikawa, Shindo, Wakabayashi, and Kageyama[21] as well as Nozoe, Matsubara, Yamamoto, and Takekuma[12g] undertook a polybromination study of the parent azulene **79** with different bromination reagents under various conditions. In most cases, the reaction with NBS, bromine and pyridinium hydrobromide perbromide rapidly afforded a quantitative yield of 1,3-dibromoazulene (**110**) via 1-bromoazulene **109**. When the NBS-polybrominated (3 molar amounts of NBS) product (**111**) in hexane was quenched with water, a dimeric bromoazulenone (**112**) was obtained together with **110** (Scheme 22).

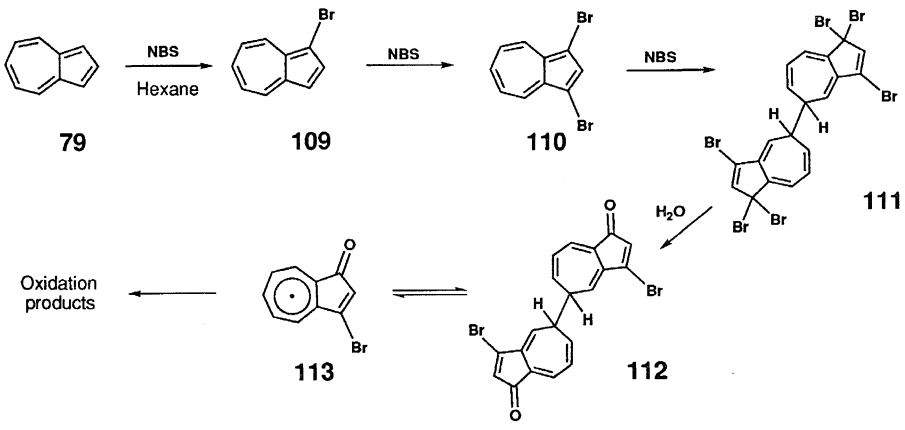
Compound **112** dissociated in an aprotic solvent to 1-oxoazulenyl radical **113**, which eventually yielded various autoxidation products in air.[12g] The behaviors of compound **112** resembled those of the aforementioned **45** obtained by the oxygenation of **13** (see Scheme 13).

With NBS in Benzene. Further, an NBS reaction of **110** in benzene gave 1,3,5-tribromoazulene (**115**) along with a small amount of tetrabromoazulene (**116**), while in acetic acid, especially in the presence of sodium acetate, the same reaction afforded 5-acetoxy-1,3-dibromoazulene (**119**) in 7% yield, besides **115**. This suggests that a bromine (1+) ion was added to C-1 of dibromoazulene (**110**) to give tribromoazulenium ion **114** followed by the addition of an acetate or bromide ion to C-5 (or C-7) of **114**, to form **117** and **118**, from which **115** and **119** were derived by HBr elimination[20,21] (Scheme 23).

The above-mentioned experimental evidence was quite different from that observed in the cases of further bromination (electrophilic substitution) of 1,3-disubstituted azulene derivatives.[22] A theoretical calculation by Kurihara et al.[20c] suggests that in the bromination



Scheme 21.



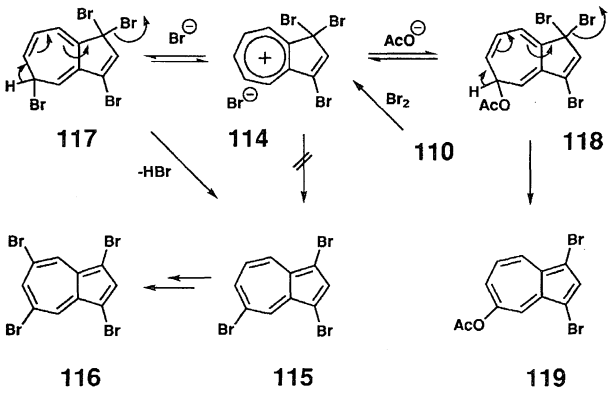
Scheme 22.

of dibromoazulene (**110**) the Br^+ should attack C-1 to give the tribromoazulenium cation **114**, whose positive charge is localized on the seven-membered ring, to undergo nucleophilic additions at C-5 and C-7 (Chart 6).

In Acetic Acid. According to a study by Nozoe, Wakabayashi, and co-workers on the polybromination of azulene (**79**) in acetic acid, a dark-green solid precipitated as a main product was considered to be a CT-complex of tribromoazulenium bromide (**114**). Furthermore, they found a mixture of ca. 1% yield of 3-bromo-1,5- (**120**) and -1,7-azulenequinones (**121**) together with trace amounts of dibromo compounds (**122** and **123**) from the mother liquor[20] (Chart 7).

In Aqueous AcOH. Then, after optimization experiments, the bromination of azulene (**79**) with 3.4 molar amounts of bromine in acetic acid containing 25% of water and quenching the reaction mixture with water overnight yielded as much as a 50% yield of a mixture of **120** and **121** together with a small amount of 3,7-dibromo-1,5- (**122**) and 3,5-dibromo-1,7-azulenequinone (**123**) and 50% of a dark reddish-violet precipitate, which was presumed to consist of a mixture of several bromobiazulene derivatives, which showed three reddish-violet spots on silica gel TLC.[20b] The structure of the top spot was identified by synthesis to be 3-(3-bromo-1-azulenyl)-1,5- (**126a**) and -1,7-azulenequinones (**126b**). The latter two spots were presumed to be a mixture of dimeric azulene derivatives (such as **127**) produced under a bromine deficient condition; by further bromination these biazulene derivatives can give additional amounts of bromoazulenequinones (**120** and **121**) via appropriate intermediates, such as **130a** and **130b** (Scheme 24).[21a] Indeed, the dark reddish-violet precipitate afforded another 30% of quinones (**120** and **121**) through repeated bromination in aqueous acetic acid. Reverse addition (the addition of azulene in aqueous THF to a bromine solution in acetic acid) also afforded ca. 80% bromoazulenequinones (**120** and **121**).[21a]

Bromine Oxidation in Aqueous THF. By carefully analyzing the above-mentioned experimental facts, Nozoe, Kageyama, and co-workers discovered a very convenient, standard procedure for a one-pot synthesis of 3-bromo-1,5- (**120**) and -1,7-azulenequinones (**121**) using aqueous THF to avoid the precipitation of a dark-violet solid.[23] Namely, a stirred solution of azulene (**79**) in 5—20% aqueous THF was added to 4.3 molar amounts of bromine in a small amount of acetic acid over a period of a few minutes at 5—10 °C, and was then quenched with water overnight. Tribromoazulenones (**132a,b**) were isolated as colorless crystals in a 1 : 1 ratio, but 3-bromo-1,5- and -1,7-azulenequinones (**120** and **121**) were obtained in a 3 : 1 ratio after quenching with water and undergoing separation by alumina column chromatography in the form of stable yellow needles. The authors have proposed possible pathways for the formation of these two bromoazulenequinones, as shown in Scheme 25.[23a]



Scheme 23.

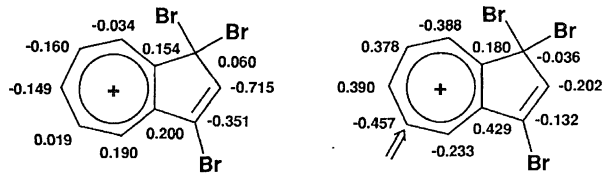


Chart 6. π-HOMO and LUMO coefficients of key intermediate **114**.

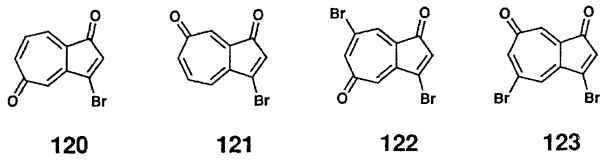
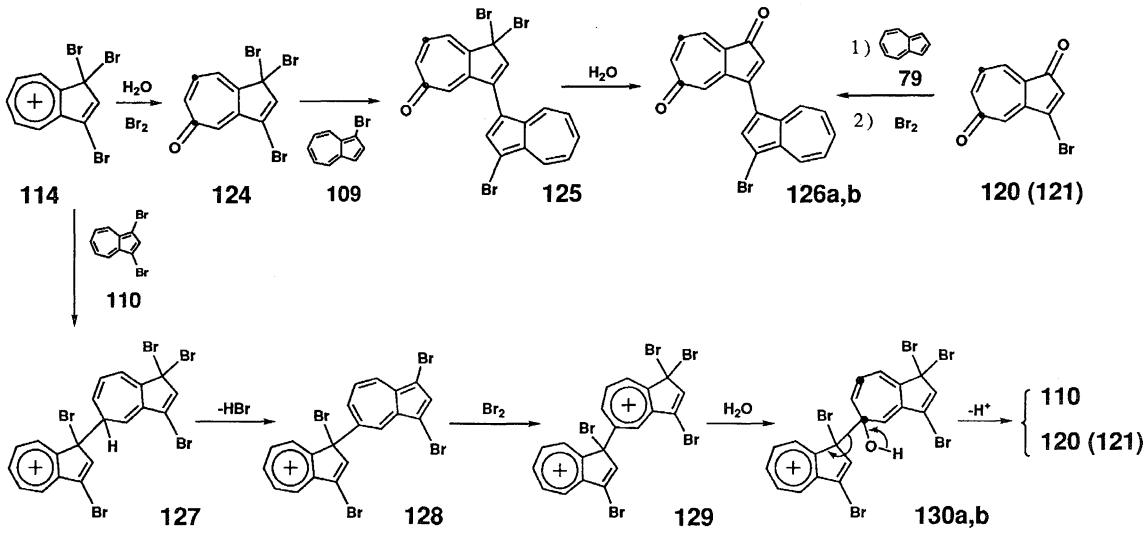


Chart 7.



Scheme 24.

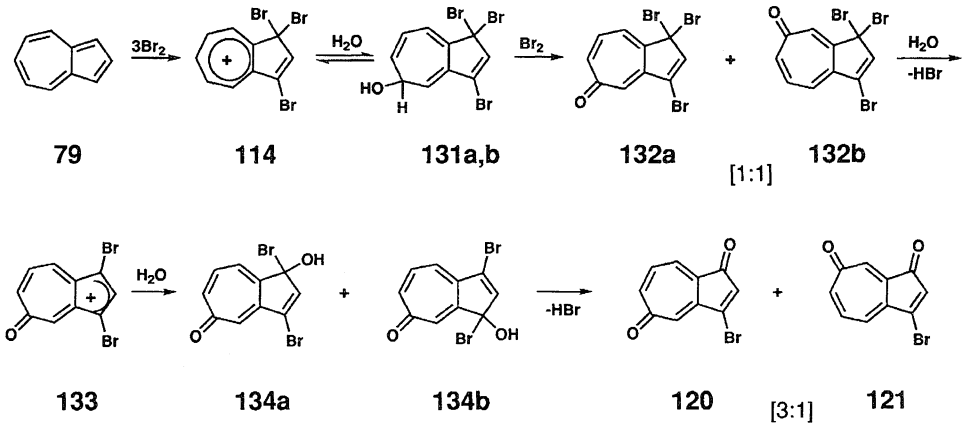
E. Scope and Limitation of the Azulenequinone Synthesis. To study the scope and limitation[21b,c] of the aforementioned one-pot azulenequinone synthesis, they used Nozoe et al.'s original method[6] and its modifications[24,25] to prepare polysubstituted azulenes as substrates. It is necessary to prepare various types of azulenequinone derivatives in order to test their biological and physiological properties as well as their solid-state electroconductivity.

Alkylazulenes without Substituents at C-1 and C-3 Positions, and 2-Phenylazulene. First, Nozoe et al. extensively studied the polybromination of 2-methylazulene (**135**) by a standard method and isolated 3-bromo-2-methyl-1,5- and -1,7-azulenequinone (**137a** and **137b**) in 45 and 15% yields, respectively. Trace amounts of bisazulenequinones (**138a**—**c**) and azulenylazulenequinones (**139a, b**) were also obtained. From the dibromo derivative (**136**) they obtained the same results, which indicate the intermediacy of this compound **136**[26a] (Scheme 26).

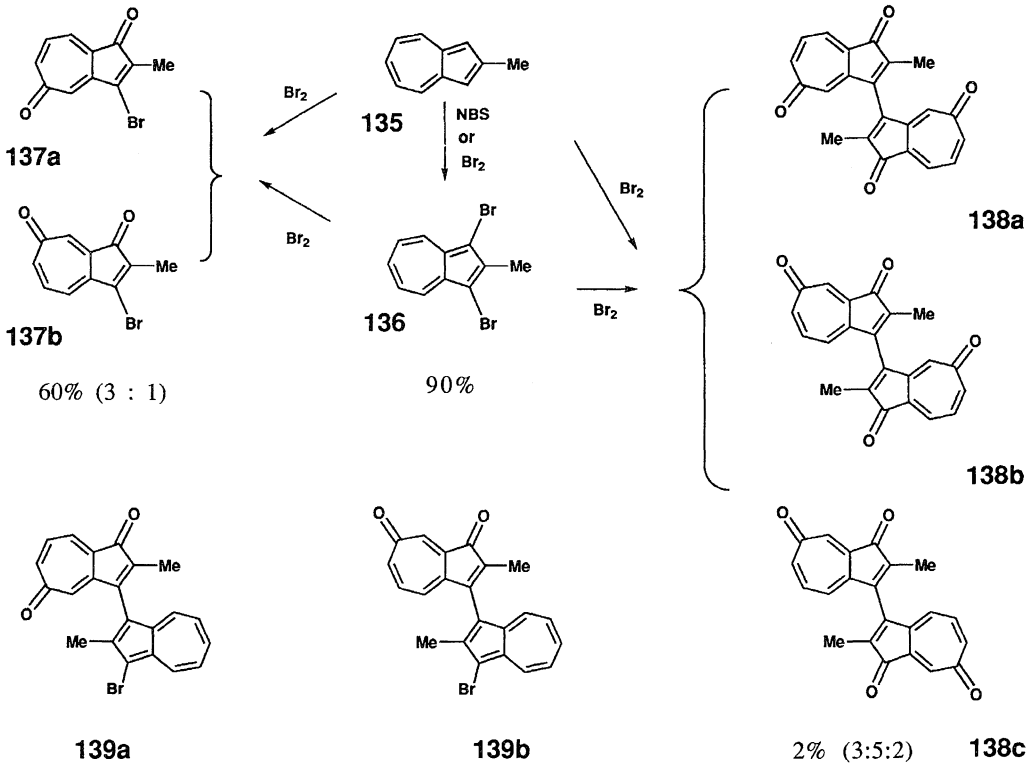
They next treated several alkylazulenes (**140**—**143**) having no substituent at the C-1 and C-3 positions and 2-phenylazulene (**144**) under the same conditions; the structures and isolated yields are shown in Table 1.[26a]

Azulene-1-carboxylic Acids. The bromine oxidation of azulene-1-carboxylic acids (**145**—**149**) without a substituent at the C-3 position afforded related 1,5- and 1,7-azulenequinones in a high yield, because a C-1 carboxylic acid group was easily substituted by bromine[26a] (Table 2).

Azulenes with Alkyl or Phenyl Group at C-1 Position. They then examined the bromine oxidation of 1-methylazulene **12** (R^1 = Me, $R^2 = R^3 = H$); however, the products were a mixture of many compounds whose structures have not yet been elucidated. Meanwhile, 1-methyl-5-isopropylazulene (**150**) gave 1-bromo-3-hydroxy-7-isopropyl-3-methyl-5(3*H*)-azulenone (**150c**) in 25% yield. However, 1-ethyl- (**151**), 1-ethyl-5-isopropyl- (**152**), 5-isopro-



Scheme 25.



Scheme 26.

Table 1. Azulenequinones from Alkylazulenes and 2-Phenylazulene without Substituents at C-1 or C-3 Position

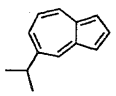
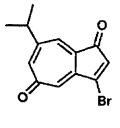
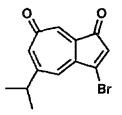
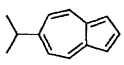
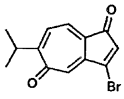
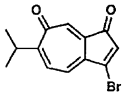
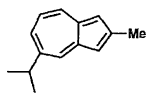
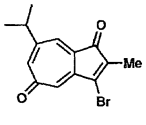
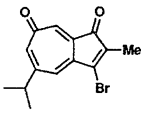
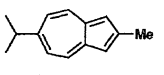
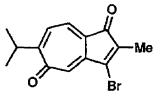
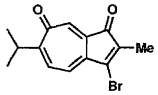
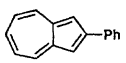
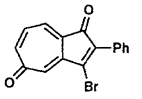
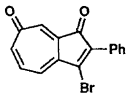
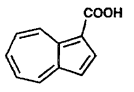
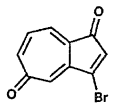
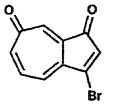
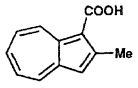
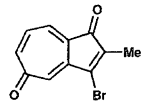
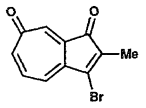
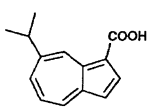
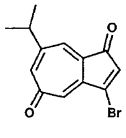
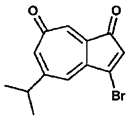
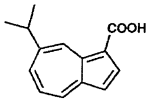
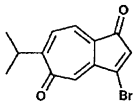
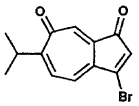
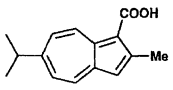
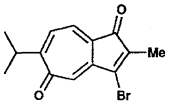
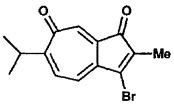
Azulenes	Azulenequinones (Yield, %)	
 **140**	 **140a** (43%)	 **140b** (15%)
 **141**	 **141a** (45%)	 **141b** (15%)
 **142**	 **142a** (48%)	 **142b** (11%)
 **143**	 **143a** (50%)	 **143b** (10%)
 **144**	 **144a** (35%)	 **144b** (10%)

Table 2. Azulenequinones from Azulene-1-carboxylic Acids[25]

Azulenes	Azulenequinones (Yield, %)	
 **145**	 **120** (43%)	 **121** (15%)
 **146**	 **137a** (45%)	 **137b** (15%)
 **147**	 **140a** (60%)	 **140b** (20%)
 **147**	 **141a** (50%)	 **141b** (15%)
 **149**	 **143a** (60%)	 **143b** (14%)

pyl-1-propylazulene (**153**) and 1-heptyl-5-isopropylazulene (**154**) unexpectedly afforded C-1 alkyl-extruded 3-bromo-1,5- and -1,7-azulenequinones together with 1-bromo-3-hydroxy-5(3*H*)-azulenone derivatives (**151c**, **152c**, **153c**, **154c**).[21c,27a]

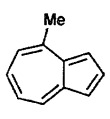
On the other hand, the bromination of 1-phenylazulene (**156**) resulted in the formation of 3-phenyl-1,5-azulenequinone (**156a**, 18%) and its 1,7-isomer (**156b**, 10%), together with two isomeric 1-bromo-3-hydroxy-5(3*H*)- and 3-bromo-1-hydroxy-5(1*H*)-azulenones (**156c** and **156d**, 60%). Upon heating of **156c,d** in the presence of a trace of concd H_2SO_4 in methanol for one day, a mixture of azulenequinones (**156a,b**) was obtained in 80% yield (1 : 1 ratio)[21c,27a] (Table 3).

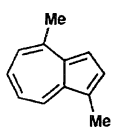
1,2-Polymethyleneazulenes. For the purpose of clarifying the mechanism of the aforementioned extrusion of C-1 substituents to give azulenequinone derivatives, Nozoe, Wakabayashi, Yang, and co-workers studied the bromine oxidation of 7-isopropyl-2,3-dihydro-1*H*-cyclopenta[*a*]azulene (**157**) and 2,3,4,5-tetrahydro-1*H*-cycloheptaazulene (**160**). Compound **157** afforded 3-(3-bromo-5-isopropyl-1,7-dihydro-1,7-dioxoazulen-2-yl)propanal (**158**) in 28% yield together with 9-bromo-7-isopropyl-3a-hydroxy-2,3-dihydro-1*H*-cyclopenta[*a*]azulen-5(3a*H*)-one (**159**, 20%) (Scheme 27), while **160** afforded 3-bromo-1,5-azulenequinone (**161a**, 18%) and its 1,7-isomer (**161b**, 6%) having a 4-formylbutyl group at the C-2 position accompanied by the corresponding hydroxyazulenone (**163**)[29a] (Scheme 28).

A treatment of **160** with 5 molar amounts of bromine gave the corresponding bromoazulenequinones (**162a,b**) having a pentanoic acid side chain in 21 and 7% yields, respectively. These experimental facts suggested that a cleavage of the C–C bond at the C-1 position took place, as shown in Schemes 27 and 28. The extrusion of an alkyl group at C-1 of **151**—**155** presumably took place in a similar manner.[21c,27a]

Azulenes with Methyl Group at C-4 Position. 4-Methyl- (**164**) and 1,4-dimethylazulene (**165**) afforded several azulenequinones as a mixture. Being unstable in air, **164** changed to a polar green compound.[27b] The bromination of 4,6,8-trimethylazulene (**14**) afforded a mixture of 1,5- and 1,7-azulenequinones (**16** and **17**) accompanied by some unidentified products. The yields of **16** and **17** were not reproducible. That may have been because of the easy bromination of methyl side chains of **14**[27a] (Chart 8).

Guaiazulene. As mentioned before, the reactions of guaiazulene **13** are sometimes quite different from those of other azulenes. Nozoe, Shindo, and co-workers found that the bromination of **13** by the standard bromine oxidation procedure with 3.2 molar amounts of bromine in aqueous THF afforded 2—6% of azulenequinone (**15**) and 10—15% of 3-bromo-1-hydroxyguaiazulen-5(1*H*)-one (**170**) as well as 60—70% of a dark-green solid **A**. The crystal structure of the compound **170** was determined by an X-ray crystallographic method. When this bromination was carried out at −5 °C with 3.2 molar amounts of bromine and the products were


164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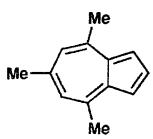
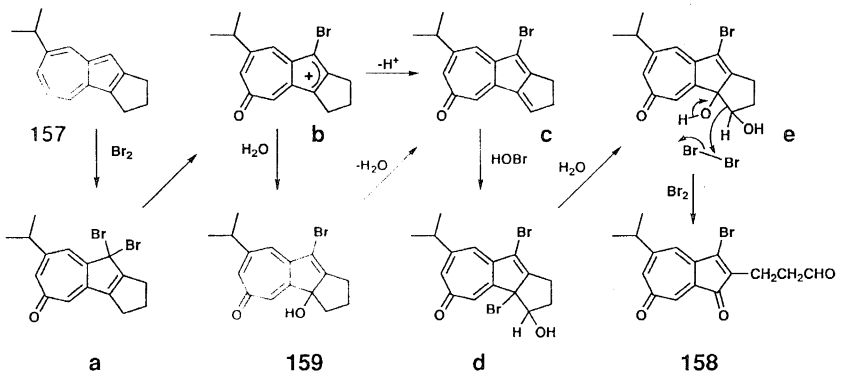
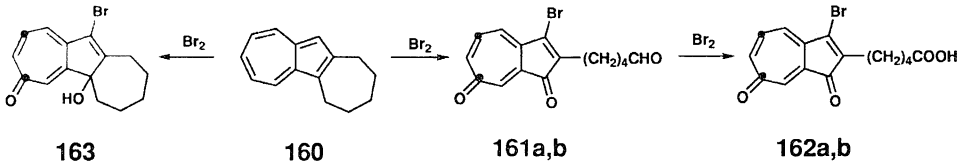

14

Chart 8.



Scheme 27.



Scheme 28.

Table 3. Azulenequinones from 1-Alkyl-, 1,5-Dialkyl, and 1-Phenylazulenes[26a,b]

Azulenes	Azulenequinones (Yield, %)		3-Bromo-1-hydroxy-azulenones	
150			**150c** (25)	
151	**120** (37)	**121** (13)	**151c** (5)	**151d** (14)
152	**140a** (20-40)	**140b**	**152c** (15)	
153	**140a** (20-30)	**140b**	**153c** (10)	
154	**154a** (22)	**154b** (10)	**154c** (5)	
155	**120** (14, 3:1)	**121**	**155c** (12)	**155d** (30)
156	**156a** (18)	**156b** (10)	**156c** (30)	**156d**

isolated without evaporation of THF, 8% of azulenequinone (**15**) and 60% of **170** were obtained without **A**. A treatment of **170** in THF in the presence of a trace amount of trifluoroacetic acid gave 24% of azulenequinone (**15**) (presumably via **166**—**168**) and 9% of the side-chain brominated azulenequinone (**171**) and pigment **A**. It should be noted that the bromide ion produced by the hydrolysis of the Br-atom at the C-3 of **170** substituted at the C-13 of isopropyl side-chain to give **171**[28a] (Scheme 29).

The structure of dibromoguaiazulenium bromide (**166**), which is a trialkyl derivative of parent azulenium ion (**114**), was determined with PFG (Pulsed Field Gradient)-HMBC (36 min) and PFG-HMQC (15 min) techniques at −35.2 °C[28a] (Chart 9).

Interestingly, colorless crystals of compound **170** gradually changed to the dark-green solid **A** upon standing under aerobic conditions at low temperature. With almost no changes in its appearance, **A** was no longer a single crystal, according to X-ray crystallographic measurements. Compound **170** rapidly changed to **A** upon heating at 90—95 °C. In a concentrated solution of methanol or 1,2-dichloroethane, **170** also gradually changed to **A**, quantitatively, upon standing under aerobic conditions at room temperature.[28] Although **A** was fairly soluble in methanol and ethanol, it was almost insoluble in ordinary aprotic solvents. The visible spectra of **A** showed a large peak at 760 nm, suggesting that it contains an azulene chromophore.[28a] An elemental analysis of **A** ($C_{15}H_{17}O_2Br$) gave practically the same results as that of the substrate **170**, but did not show any fragment peaks in the mass

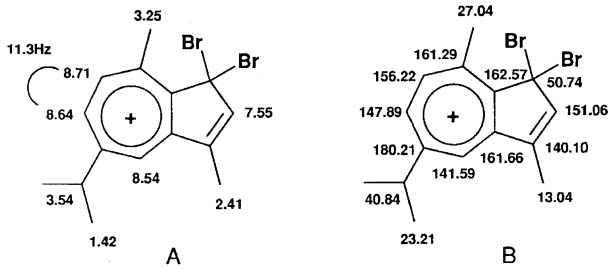


Chart 9. NMR spectra of compound **166**, A: ^{1}H NMR (400 MHz, CD_3CN), B: ^{13}C NMR (100 MHz).

spectrum. Since its NMR spectrum in CD_3OD showed no definite signal for structure deduction, **A** might be polymeric.

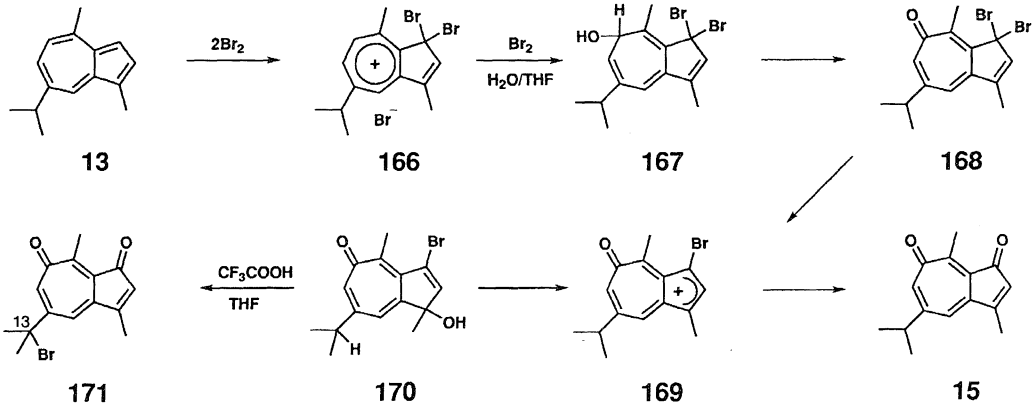
Very recently, Nozoe, Ikeda, and Takeshita[28d] reexamined the reaction of **170** and the structure of **A**. A treatment of **170** with acetic anhydride at 25 to 40 °C yielded, among a few other products, a reductive debromination product, 5-acetoxy-7-isopropenyl-1,4-dimethylazulene **174**. A possible pathway for the reaction is shown in Scheme 30.

Note that 3-bromoguaiazulene (**87**) and its derivatives have low oxidation potentials,[20d] and, as a result, its Br is gradually displaced by H (reductive debromination) in a protic solvent, such as methanol.[18b,19]

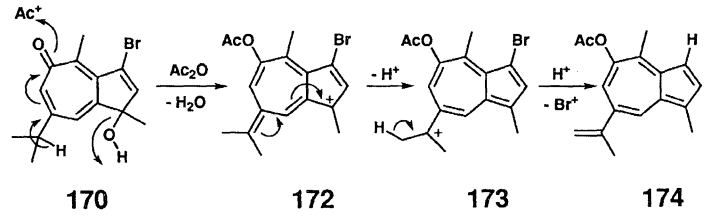
The molecular-weight distribution of **A** by means of the Gel-Filtration method indicated that **A** was a mixture of MW = 2000 to 20000. Although **A** was rather stable in a dilute solution of methanol or 1,2-dichloroethane upon standing at room temperature, the change was facilitated in the presence of benzoyl peroxide, a radical initiator, when heated in a methanol-d_4 solution at 60 °C.

Based on several findings, i.e., i) easy debromination should be characteristic for only guaiazulene derivatives,[18b,19] ii) retention of the bromine in **A**, and iii) a very easy formation of **A** in solid state, the change of **170** to **A** should reasonably be expressed as involving a radical mechanism, as shown in Scheme 31; the methine hydrogen of the isopropyl group was highly reactive and the tertiary hydroxyl group of **170** is allylic. Thus, **A** is a polymer having such an azulene structure as **176**, although the structure remains to be investigated further.

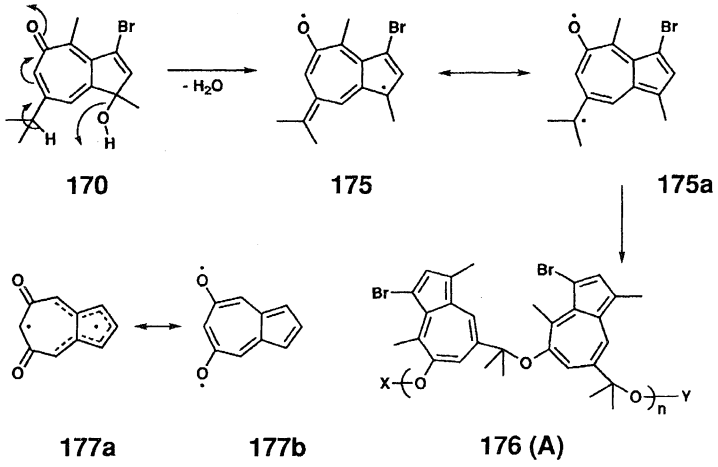
It is noted that intermediate **175** corresponds to a derivative of very reactive non-Kekulé 5,7-azulenequinone (**177**), which should react as a biradical.[2] Figure 1 shows the X-ray crystal structure of **170**, a head-to-tail overlapping pair within a lattice.[28b,c] Interestingly, the reactive sites, namely the *t*-hydroxyl group and the methine hydrogen of the isopropyl group in **170**, are located within a very close range. This might be the reason for the easy dehydration followed by the polymerization of **170**, even in the solid state.



Scheme 29.



Scheme 30.



Scheme 31.

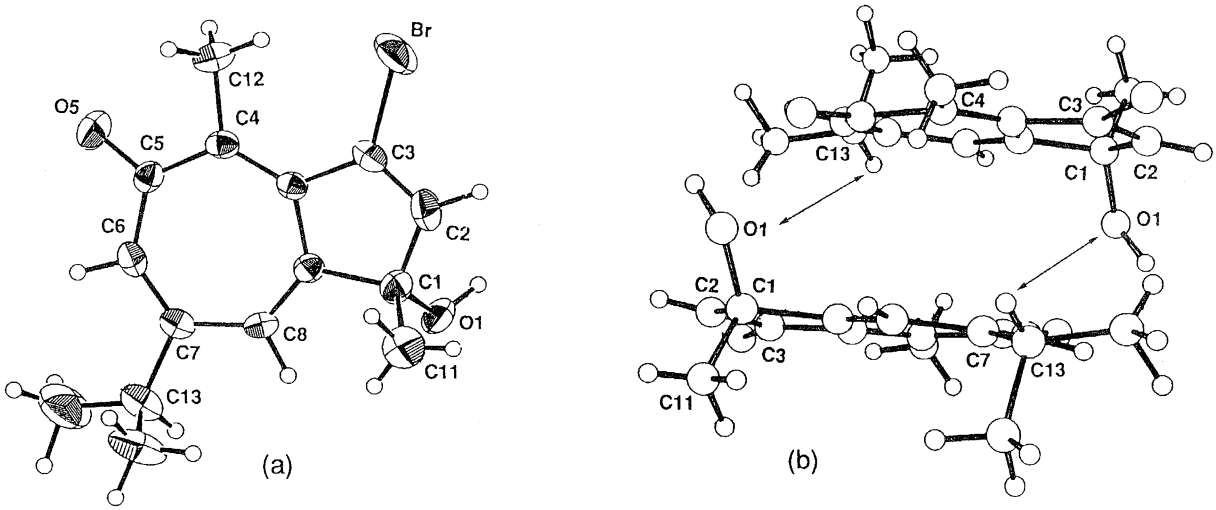


Fig. 1. (a) X-Ray crystal structure of compound **170**, and (b) Stereoview of the paired **170** in the crystalline packing, where the methine H on the isopropyl group and the *t*-OH locate in a close position.

Polymerization via C–C bond-making through the **177**-type biradical may also be possible for the formation of **A**.

Azulenes with Various Functional Groups. According to Nozoe, Wakabayashi, Yang, and co-workers the azulenes having various functional groups usually give the corresponding azulenequinones, as shown in Table 4.[29a] It is noted, however, that methyl azulene-1-carboxylate (**181**) gave a mixture (which still remains unidentified) without the formation of azulenequinone derivatives, while its 2-methyl- (**182**) and 2-methyl-7-isopropylazulene-1-carboxylate (**183**) afforded considerable amounts of azulenequinones (**182a,b** and **183b**).

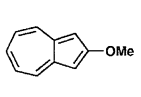
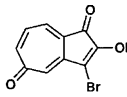
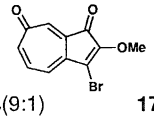
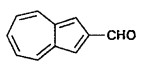
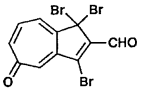
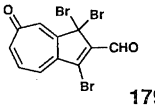
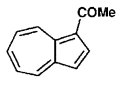
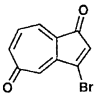
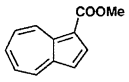
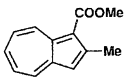
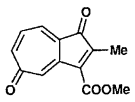
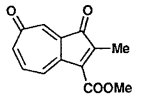
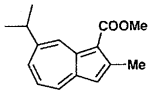
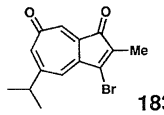
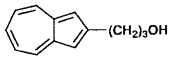
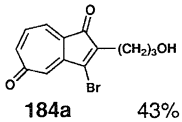
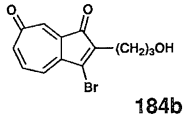
Fujimori et al.[31] obtained tribromoketones (**179a,b**); they presumed that saponification of the *gem*-dibromo group was difficult under this condition. A propyl alcohol side-chain at C-2 of the azulene **184** was not changed by this method.

Haloazulenes. When Nozoe, Wakabayashi, and co-workers treated 1,3-difluoroazulene (**186**)[29a] by a standard method, isomeric fluoroazulenequinones (**186a** and **186b**) were confirmed by MS. However, these compounds were so unstable and saponifiable that they gave dark insoluble compounds. Tsunetsugu et al.[30] obtained various di- (**122** and **123**) and tribromoazulenequinones (**189a** and **189b**) in reasonable yields by treating 1,3,5-tribromoazulene (**115**) with pyridinium hydrobromide perbromide in aqueous acetonitrile. The results of the synthesis of various haloazulenequinones are shown in Table 5.

Heterocycle-Annulated Azulenes. Fujimori, Yasunami, and Nozoe[31] obtained various azulenequinone derivatives from the azulene derivatives annulated with thiophene (**190** and **191**) and furan rings (**192**), as shown in Scheme 32. On the contrary, dihydrofuran- and dihydrothiophene-annulated compounds did not give azulenequinones under the same conditions.

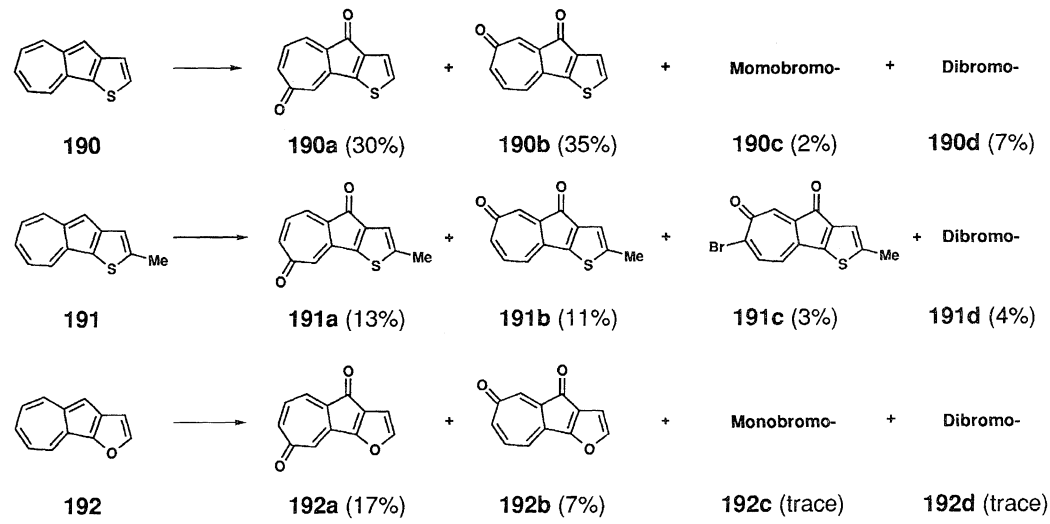
F. Nucleophilic Substitution of Bromoazulenequinones. 3-Bromo-1,5- and -1,7-Azulenequinones. Pure 3-bromoazulenequinones (**120** and **121**) are stable upon standing in the air or at 150 °C. However, these compounds are very easily hydrolyzed with alkali at low temperature, or even by heating with 1,4-dioxane-water at 80 °C, to give a dark-brown or almost black insoluble solid. An intensive study has shown that an initial product, 3-hydroxy-1,5-azulenequinone (**193**), soon polymerized to a dark solid. Although Nozoe et al.[32a] first considered this solid to be a linear H-bonded polymer, the reaction path for the formation of polymer **195**, shown in Scheme 33, appears to be more reasonable.[32b]

Table 4. Azulenequinones from Azulenes with Various Functional Groups

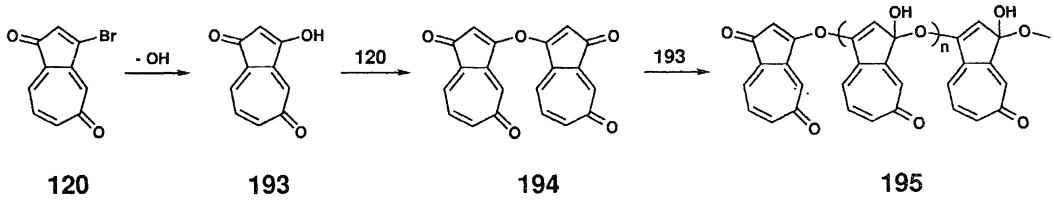
Azulenes	Azulenequinones (Yield, %)		
 **178**	 **178a**	25%(9:1)	 **178b**
 **179**	 **179a***		 **179b***
 **180**	 **120**	73%(13:1)	 **121**
 **181**	**none**		
 **182**	 **182a**	50%(8:1)	 **182b**
 **183**		50%	 **183b**
 **184**	 **184a**	43%	 **184b**

*Products of insufficient hydrolysis.

On the other hand, they easily synthesized various 1,5- (a) and -1,7- (b) azulenequinones (**196a,b**—**207a,b**) in high yields, by the



Scheme 32.



Scheme 33.

Table 5. Azulenequinones from Haloazulenes

Azulenes	Azulenequinones (Yield, %)	
185	120	121
186	186a	186b
187	187a 80% (3:1)	187b
188	120	121
115	122 (40%)	123 (23%)
	189a (31%)	189b (16%)

reaction of a wide variety of nucleophiles with **120** and **121** as convenient synthons,[32a] as shown in Scheme 34.

Nucleophilic Substitution of Dibromoazulenequinones. Tsunetsugu, Nozoe, and co-workers studied nucleophilic displacement of 3,7-dibromo-1,5- (**122**) and 3,5-dibromo-1,7-azulenequinones (**123**).[30] In each case, 3-monosubstitution took place in a more facile way than the substitution of the bromine atom on the seven-membered moiety. The formations of mono- and di-substitution products (**208a,b**—**218a,b**) from **122** and **123** are shown in Scheme 35.

Physical Properties

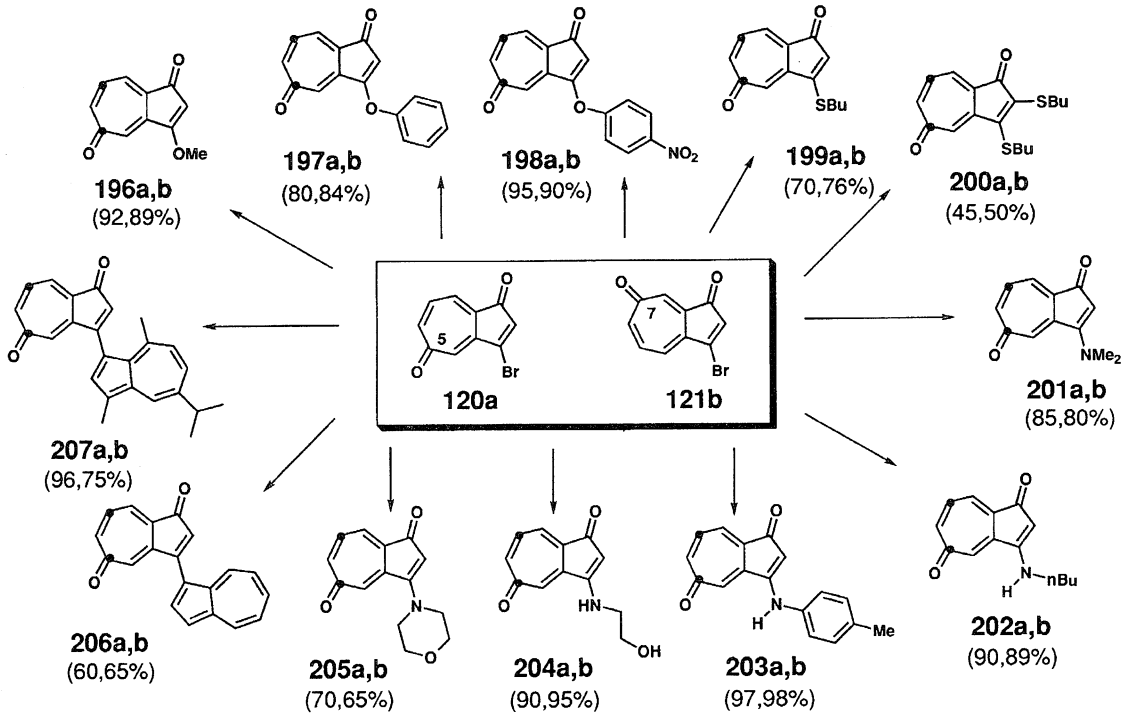
A. General Physical Properties. UV-vis Absorption Spectra. Scott[1c] reported on the absorptions of the parent 1,5- (**77**) and 1,7-azulenequinones (**78**) and several alkyl derivatives together with some theoretical discussions. The UV-vis absorption spectral curves of the parent azulenequinones (**77** and **78**) and their 3-bromo (**120** and **121**) and 3-methoxy derivatives (**196a,b**), measured by Takeshita et al., are shown in Figs. 2 and 3.[28c]

I. R. Spectra. Scott[1c] presented data together with discussions.

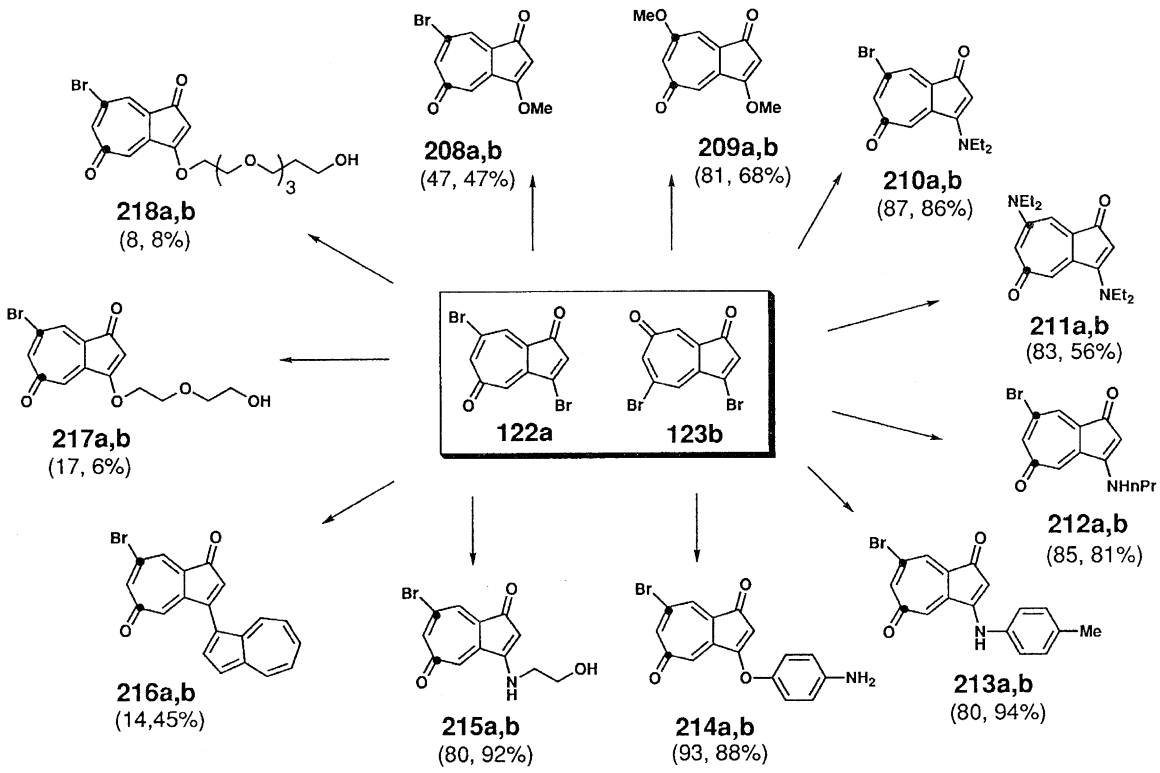
^{1}H and ^{13}C NMR. Representative data are summarized by Scott.[1c]

Mass Spectra. The spectra of 1,2-, 1,5-, and 1,7-azulenequinones are briefly presented by Scott.[1c]

B. Redox Potentials. Quinones have been known to be representative Wurster-type electron acceptors, and have been used as oxidizing agents for many years. It is therefore of interest to consider here the redox behavior of azulenequinones in order to compare them with benzenoid quinones.



Scheme 34.



Scheme 35.

The redox potentials of the parent 1,5- (**77**) and 1,7-azulenequinone (**78**), as well as their 18 substituted derivatives, were measured by cyclic voltammetry in MeCN by Suzuki et al. The important values are summarized in Table 6.[33]

These novel azulenequinones are moderate electron acceptors (E_1^{red}: −0.8 — −1.2 V), anthraquinone (E_1^{red}: −0.95 V), and are slightly weaker than the isomeric naphthoquinone (E_1^{red}: −0.71 V). In favorable cases, such as 3-methoxy-1,7-azulenequinone (**196b**), the voltammograms exhibited two pairs of quasi-reversible waves, corresponding to two-stage one-electron reductions of the quinones (Fig. 4a).

However, probably due to the kinetic instability of the

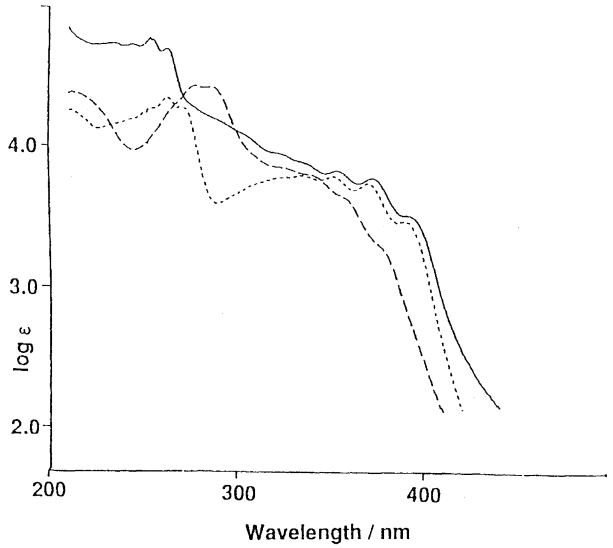


Fig. 2. Electronic absorption spectra of **77** (—), **120** (···), and **196a** (- - -) in acetonitrile.

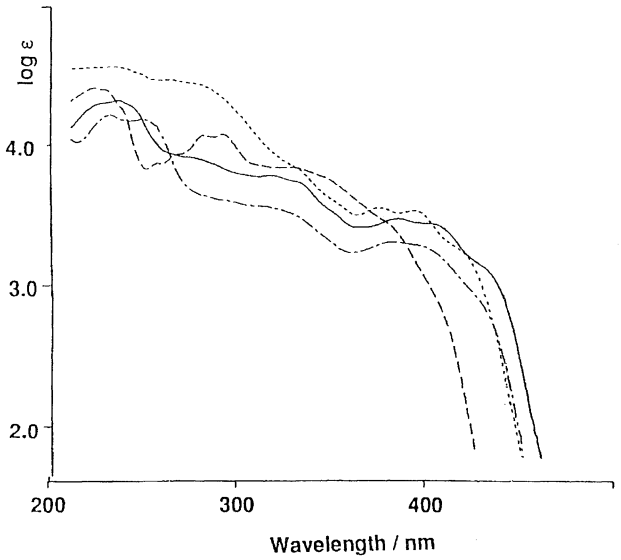
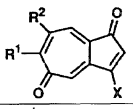
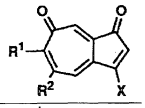


Fig. 3. Electronic absorption spectra of **78** (—), **121** (···), **196b** (- - -), and **15** (– · –) in acetonitrile.

anion-radical species, the reduction waves were irreversible in most cases, which prevented quantitative comparisons of these values. In any case, it was clearly shown that the electron affinities of the 1,5- (E_1^{red}: −0.86 V) and 1,7-azulenequinone (E_1^{red}: −0.86 V) are close to each other. Since both skeletons are electronically perturbed by the substituent in a similar manner, the difference in E_1^{red} is negligible for many combinations of compounds having the same substituent (e.g. **120** vs. **121**). Although the quinones (**77**, **78**, **120a,b**, **196a, b**, **141a,b**, and **140a,b**) do not undergo one-electron oxidation up to +2.0 V, the electrochemical amphotericity could be induced by substituting a strong electron-releasing group, such as an amino group. Thus, 3-dimethylamino derivatives (**201a,b**, **219a,b**, and **220a,b**) were oxidized at around +1.3 V, showing that their HOMO levels are as high as that of *o*-dimethoxybenzene (E_1^{ox}: +1.35 V). Although the secondary

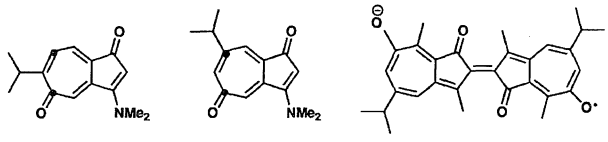
Table 6. Redox Potentials Measured in MeCN (*E*/V vs. SCE)[a)]

X	R^1	R^2		
H	H	H	**77** E_1^{red}: −0.86* E_1^{ox}: > +2.0	**78** E_1^{red}: −0.86* E_1^{ox}: > +2.0
Br	H	H	**120** E_1^{red}: −0.78* E_1^{ox}: > +2.0	**121** E_1^{red}: −0.78* E_1^{ox}: > +2.0
Br	*i*-Pr	H	**141a** E_1^{red}: −0.82* E_1^{ox}: > +2.0	**141b** E_1^{red}: −0.82* E_1^{ox}: > +2.0
Br	H	*i*-Pr	**140a** E_1^{red}: −0.81* E_1^{ox}: > +2.0	**140b** E_1^{red}: −0.79* E_1^{ox}: > +2.0
OMe	H	H	**196a** E_1^{red}: −1.07* E_1^{ox}: > +2.0	**196b** E_1^{red}: −1.11 E_1^{ox}: > +2.0
$N(CH_3)_2$	H	H	**201a** E_1^{red}: −1.20* E_1^{ox}: +1.34*	**201b** E_1^{red}: −1.20* E_1^{ox}: +1.31*
$N(CH_3)_2$	*i*-Pr	H	**219a**[$] E_1^{red}: −1.27 E_2^{red}: −1.66* E_1^{ox}: +1.28*	**219b**[$] E_1^{red}: −1.29 E_2^{red}: −1.60* E_1^{ox}: +1.25*
$N(CH_3)_2$	H	*i*-Pr	**220a**[$] E_1^{red}: −1.26 E_2^{red}: −1.63* E_1^{ox}: +1.31*	**220b**[$] E_1^{red}: −1.27 E_2^{red}: −1.58* E_1^{ox}: +1.29*
$NH(CH_2)_2OH$	H	H	**204a** E_1^{red}: −1.20* E_1^{ox}: +1.6**	**204b** E_1^{red}: −1.19* E_1^{ox}: +1.4**
	H	H	**203a** E_1^{red}: −1.1** E_1^{ox}: +1.4**	**203b** E_1^{red}: −1.14* E_1^{ox}: +1.5**

a) All the values in this and in text were measured under the identical conditions (0.1 M Et_4NClO_4 Pt electrode, 100 mV s^{-1}) (M=mol dm^{-3}). *; Irreversible waves, and the values are calculated as $E^{red} = E_p + 0.03$ and $E^{ox} = E_p - 0.03$. **; Waves are so broad that only the approximate values are available. $; Unpublished.

amine derivatives (**203a,b** and **204a,b**) were also proven to be amphoteric, the oxidation waves were so broad that the values of E_1^{ox} are ambiguous. The introduction of an isopropyl group did not change the essential redox properties of the skeleton, but only affected the potentials as a weak electron-donating group (Chart 10).

Guaiazulenequinone (**15**) is also one interesting member of 1,7-azulenequinones,[34)] which underwent two reversible one-electron reductions at −1.13 and −1.52 V. The biguaiazulenequinone (**47**) inherits its characteristic redox behavior from **15**, and its voltammogram showed three pairs of reversible waves at −1.02, −1.18, and −1.47 V (Fig. 4b). Both the first and second waves correspond to E_1^{red} of **15**, and



219a,b **220a,b** **47a**

Chart 10.

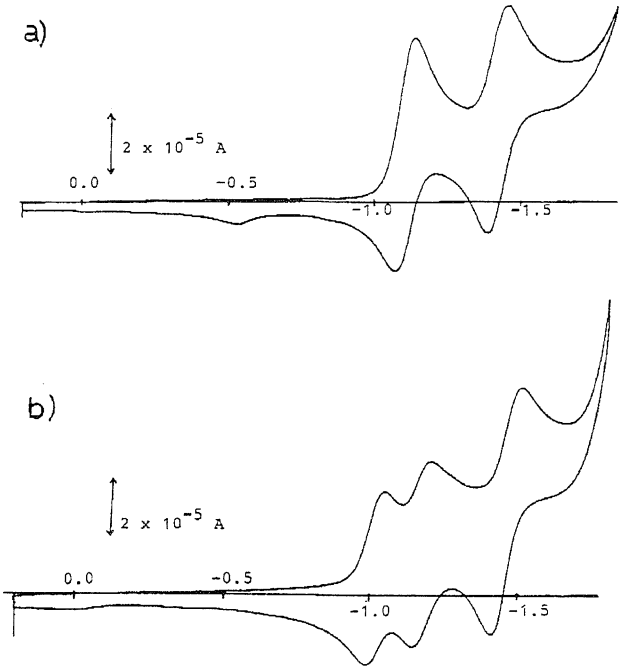


Fig. 4. Cyclic voltammograms of (a) 3-methoxy-1,7-azulenequinone (**196b**), and (b) biguaiazulenequinone (**47**) measured in MeCN containing 0.1 mol dm^{-3} Et_4NClO_4 as a supporting electrolyte (*E*/V vs. SCE, Pt electrode).

the third one is a two-electron process, where both quinone units in **47** are reduced to dianion. The observed separation between E_1^{red} and E_2^{red} at least indicates the electronic communication of the two azulenequinone units in **47**, and suggests the contribution of form **47a** for the anion-radical species (Chart 10).

The above-mentioned features show the intriguing redox properties of the novel azulenequinones, which serve as new candidates for the construction of multi-redox systems exhibiting interesting electronic and optical properties.

C. X-Ray Crystallographic Analysis. 3-Chloro-1,5- and 1,7-Azulenequinones. In the crystallographic structures of **187a** and **187b**, very interesting features have been found, as shown in Fig. 5 (a,b) and Fig. 6 (a,b).[35] The coplanar molecules are connected by several short CH···O hydrogen bonds. Additionally, there exist electrostatic interactions through the CH···Cl and Cl···Cl contacts.[36] Thus, molecules form tight "sheet" structures consisting of close networks. On the other hand, the sheets are stacked at short and equivalent intervals, and there exist some effective π–π overlapping of the azulenequinone skeleton. Such a phenomenon, arising by self-assembly due to various types of weak, but attractive, interactions, has recently drawn much attention in solid state chemistry.

Guaiazulenequinone. An ORTEP drawing of two crystallographically independent molecules of **15** is shown in Fig. 7.[34] Although the substituents of **15** might prevent the azulenequinone skeleton from such an aggregation in a crystal, a suitable molecular arrangement for the CH···O interaction was also observed in the highly alkylated 1,7-azulenequinone derivative, guaiazulenequinone **15**.[34]

D. Theoretical Considerations. Scott et al.[2] predicted the physical and chemical properties of sixteen possible structures of azulenequinones in terms of thermodynamic stability, electron affinity, reduction potential, charge-transfer complex, Michael addition, dimerization, polymeriza-

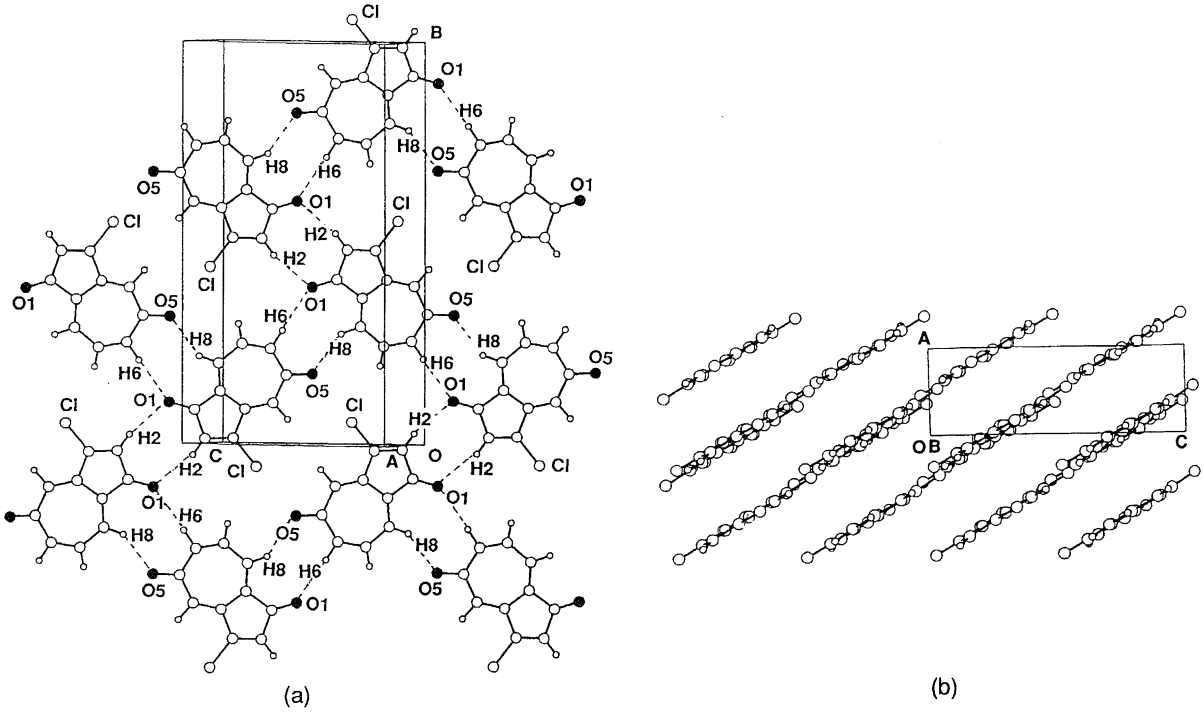


Fig. 5. X-Ray crystal structure of compound **187a** (a) "Sheet" like networks by O···H hydrogen bondings. (b) Stacks of "Sheet" like networks.

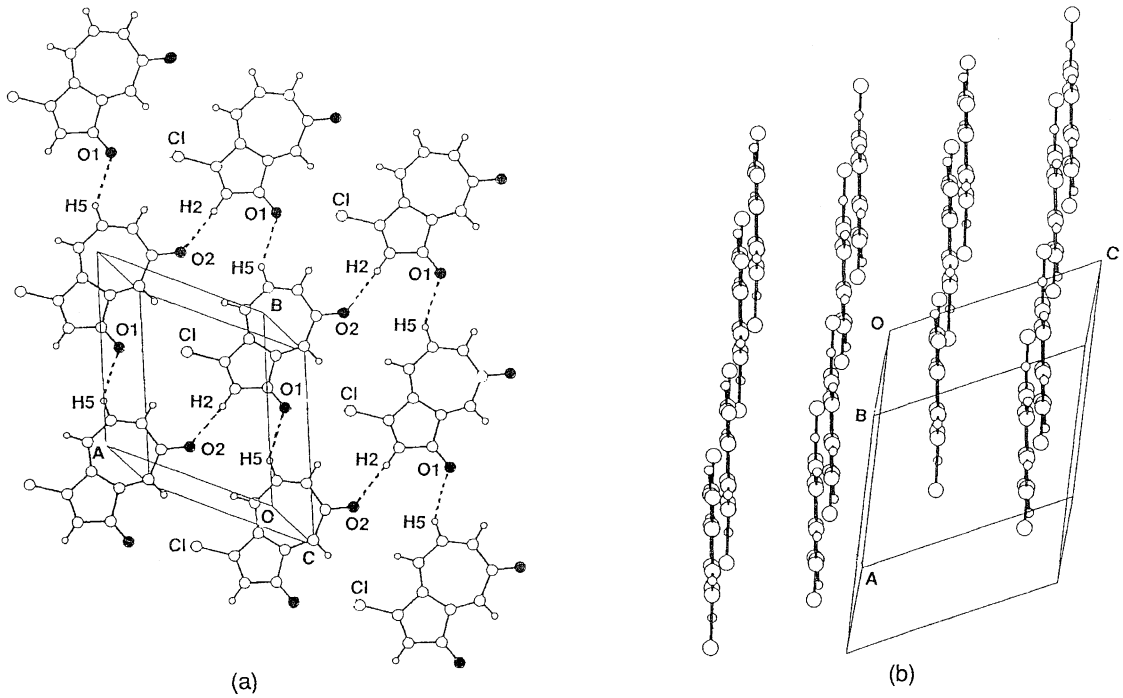


Fig. 6. X-Ray crystal structure of compound **187b**. (a) "Sheet" like networks by O···H hydrogen bondings. (b) Stacks of "Sheet" like networks.

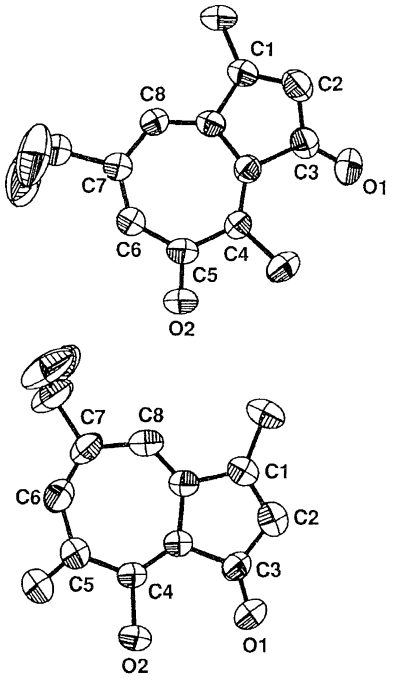
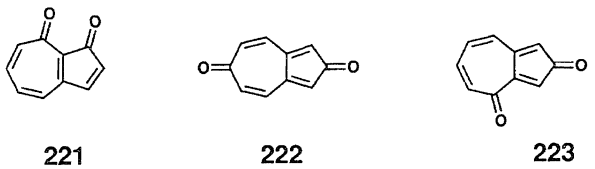


Fig. 7. X-Ray crystal structure of compound **15**.



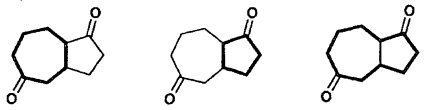
221 **222** **223**

Chart 11.

Table 7. Resonance Energies and Circuit Resonance Energies of Azulenequinones

Compd	RE[a]	CRE[b]			ΔH_f[c]
		r_1	r_2	r_3	
31a	0.0331	0.0509	−0.0190	0.0059	−0.4
71a	0.0028	0.0458	−0.0511	0.0099	−0.8
77	0.0425	0.0482	−0.0168	0.0093	−6.4
71b	0.0031	0.0463	−0.0521	0.0102	−0.6
78	0.0423	0.0482	−0.0168	0.0091	−5.3
221	0.0036	0.0451	−0.0502	0.0106	−0.6
222	−0.0355	0.0079	−0.0057	0.0132	4.7
223	−0.0353	0.0070	−0.0495	0.0137	4.7

a) Resonance energy (in β unit). b) Circuit resonance energy (in β unit).



r_1 r_2 r_3

c) Heats of formation (kcal mol^{-1}) by means of MINDO/3 method (cf. Ref. 2).

tion, and color, etc. based on theoretical calculations. They reported that the azulenequinones which contain a tropone ring (**77** and **78**) are more stable than those which contain a cyclopentadienone ring (**222** and **223**); those which contain both types of annulenone ring (**71a,b** and **221**) fall in between. (Chart 11)

Kurihara et al.[37] also predicted the stability of azulenequinones in terms of Aihara's topological resonance energies (TRE).[38] The calculated resonance energies and circuit resonance energies for azulenequinones are given in Table 7. From the calculated circuit resonance energies, the tropone

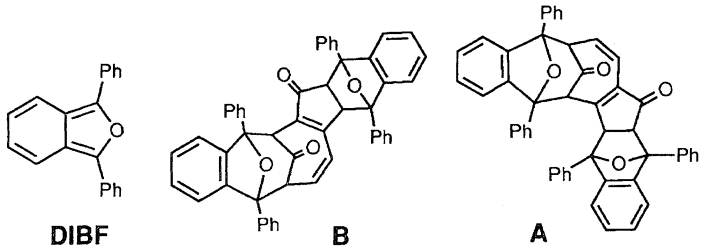
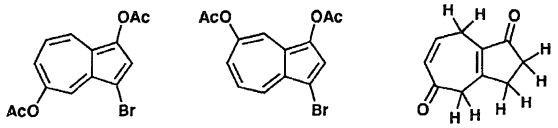


Chart 12.



Scheme 36.

ring (r_1) is predicted to be aromatic, with a positive resonance energy; however, the cyclopentadienone ring (r_2) is predicted to be antiaromatic, with a negative resonance energy.

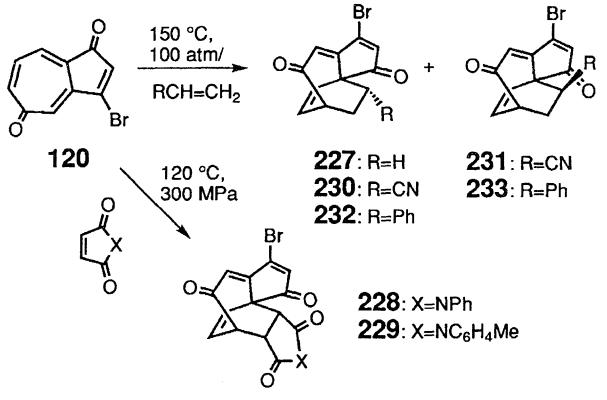
Chemical Reactions

A. Reductive Acetylation and Debromination. Sufficiently purified 3-bromo-1,5- (**120**) and -1,7-azulenequinone (**121**) are stable at a high temperature of 150 °C. Upon reductive acetylation, both compounds afforded 3-bromo-1,5- (**224**) and -1,7-diacetoxyazulenes (**225**) in 45 to 50% yields, together with reduced products, while compound **120** gave dienedione **226** with Zn dust in acetic acid at room temperature[23a] (Scheme 36), Nozoe, Wakabayashi, and coworkers obtained parent azulenequinones (**77** and **78**) by a treatment of **120** and **121** with tin powder in acetic acid in ca. 30% yield. Later, Takeshita, and Nozoe obtained the parent azulenequinones (**77** and **78**) in ca. 80% yield by a catalytic reduction of **120** and **121** with a Pd–C catalyst.

B. Thermal Cycloadditions. The azulenequinones, belonging to extended quinones, are isomeric to naphthoquinones, such as 2,6-naphthoquinone, and hitherto prepared azulenequinones are all tropone derivatives having no cyclopentadienone unit.[1,16b] Therefore, the chemical properties of the azulenequinones should be compared with those of the tropones. One of the most characteristic chemical properties of the tropones is cycloadditions.[39] The tropones behave as cycloaddends, both with dienes and dienophiles, of 2π-,[40a,b,41] 4π-,[40c] 6π-,[40d] and 8π-components[40f] depending upon the properties of the counterparts. Reflecting the electron-deficient conjugated π-electron structures, the electron demand of the cycloadditions as a diene component is usually according to an inverse manner.[40g]

Consequently, the cycloadditions of the azulenequinones should be similar to those of the tropones perturbed with further electron-withdrawing carbonyl substituents. At the same time, in azulenequinones, there are two different reaction modes within the same electrocyclic paths, one of which, however, should result in the generation of the cyclopentadienone chromophore. This would regulate the direction of the reaction sites in the azulenequinones; in the monocyclic tropones, equally possible reaction paths should give two isomers of the same electrocyclic product. Indeed, by 1984, Scott and Adams[16b] had already observed the formation of a single product from the reaction of each 1,5- (**77**) and 1,7-azulenequinone (**78**) with 1,3-diphenylisobenzofuran (DIBF). In addition, the reactivity of the cycloadditions of the azulenequinones should be enhanced under the high-pressure conditions, like the tropones.[42a,b] The utilities of high-pressure cycloadditions in tropones are well recognized despite an early study by le Noble and Ojosipe, who predicted a slight pressure acceleration[42c] (Chart 12).

With Dienophiles. The cycloadditions of 3-bromo-1,5- (**120**) and -1,7-azulenequinone (**121**)[32a] with various cycloaddends generally give [2+4] cycloadducts;[43] the cycloadditions of bromoazulenequinones were inert under atmospheric pressure; they were thus examined under high-pressure conditions. Upon heating at 100 °C in an autoclave (2 MPa), **120** with ethene gave a single Diels–Alder 1 : 1-adduct (**227**), a condensed dihydrohomobarrelenone; the addition had occurred to avoid the generation of the cyclopentadienone chromophore (Scheme 37). With electron-withdrawing dienophiles, **120** smoothly afforded 1 : 1-Diels–Alder adducts under 300 MPa; *N*-phenylmaleimide



Scheme 37.

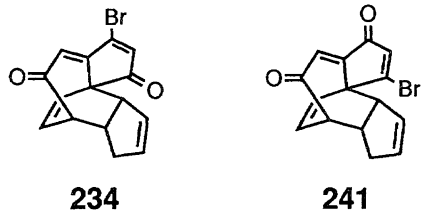


Chart 13.

and *N*-(*p*-tolyl)maleimide afforded 1 : 1-[4+2] cycloadducts (**228** and **229**), respectively.

On the other hand, the reaction of **120** with unsymmetrical dienophiles, acrylonitrile, and styrene, gave stereoisomeric 1 : 1-[4+2] adducts (**230** and **231**) and (**232** and **233**), respectively. The reaction was regioselective, but not stereospecific. With cyclopentadiene, **120** afforded only a single [4+2] cycloadduct (**234**) (Chart 13).

Under similar conditions, **121** with ethene and *N*-phenylmaleimide also gave single 1 : 1-[4+2] adducts (**235** and **236**). With acrylonitrile and styrene, it gave stereoisomeric 1 : 1-[4+2] adducts (**237** and **238**) and (**239** and **240**), respectively (Scheme 38).

With **121** cyclopentadiene again behaved as a dienophile to afford a single 1 : 1-[4+2] cycloadduct (**241**), having the same regiochemistry as the products derived from **120**.

Consequently, the regiospecific formation of the 1 : 1-[4+2] cycloadducts from bromoazulenequinone was electronically controlled to yield no cyclopentadienone chromophore.

Diphenylisobenzofuran. According to Scott et al., the Diels–Alder reactions of 1,5-azulenequinone (**77**) and 1,7-azulenequinone (**78**) with DIBF[16b] gave the sole 1 : 2-[2+4]–[6+4] cycloadducts, of which the stereochemistry was, however, not defined. It is desirable to extend the reaction of bromoazulenequinones to that with DIBF.

The heating of a mixture of **120** and DIBF at 130 °C in chlorobenzene under atmospheric pressure afforded three products: 1 : 1-[2+4] cycloadduct (**242**) and two 1 : 2-cycloadducts (**243** and **244**).[44] The further reaction of **241** with DIBF afforded **243** and **244** in improved yields (Chart 14).

Both **243** and **244** contained only one carbonyl group, and the tropone carbonyl was involved in the reaction. An X-ray crystallographic analysis of **243** elucidated the full stereochemistry; its ORTEP diagram is shown in Fig. 8.

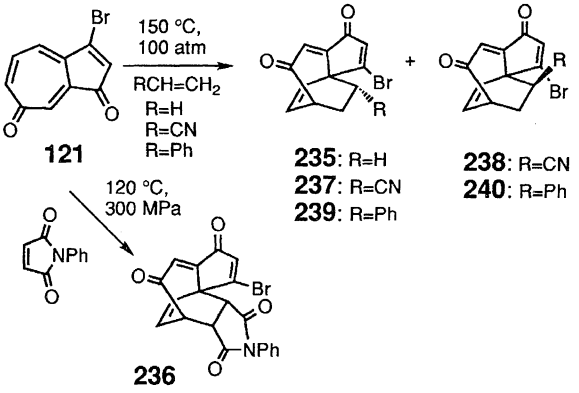
In view of the thermally disallowed [8+4] structures for **243** and **244**, the spirocyclic [2+4]–[2+4] cycloadducts (**245** and **246**), for which the tropone carbonyl served as the 2π component, were proposed to be the precursors. Previously, the tropone carbonyl had not been involved in the [2+4] cycloaddition,[40f] unlike in the case for the C=S group of tropothione, as reported by Machiguchi et al.[45] (Scheme 39).

A similar reaction of **121** with DIBF at 130 °C in chlorobenzene gave two 1 : 2-[2+4]–[6+4] cycloadducts (**247** and **248**) (Chart 15). Their structures were established by an X-ray crystallographic analysis of **248**, as shown by the ORTEP diagram in Fig. 9.

With unsubstituted 1,5-azulenequinone (**77**), DIBF yielded a 1 : 2-product (**249**) and a 1 : 1-product (**250**);[46] **249** seems to be identical to Scott's product with respect to the ^{1}H NMR spectrum. The *anti-exo*-[6+4]–*endo*-[2+4] structure for **249** was elucidated from NMR spectral comparisons with a series of cycloadducts obtained from bromoazulenequinones.

Surprisingly, **249** was partially cycloreversed to **250**. Even under the work-up conditions (silica-gel column chromatography) or standing in a benzene solution, **249** was converted into **250** and DIBF. Thus, the [2+4] moiety in **249** was changed to the [6+4] mode in **250** (Scheme 40).

On the other hand, DIBF with 1,7-azulenequinone (**78**) afforded two 1 : 2-[2+4]–[6+4] cycloadducts (**251** and **252**, Chart 16).[46] With respect to an ^{1}H NMR spectral comparison, the minor product **252** was identical with the product isolated by Scott,[16b] and the other, **251**, was its stereoisomer. A



Scheme 38.

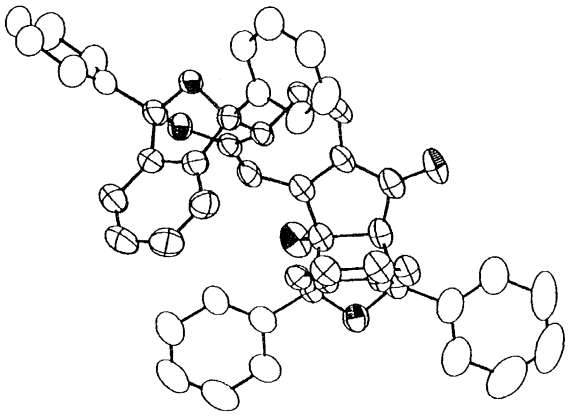
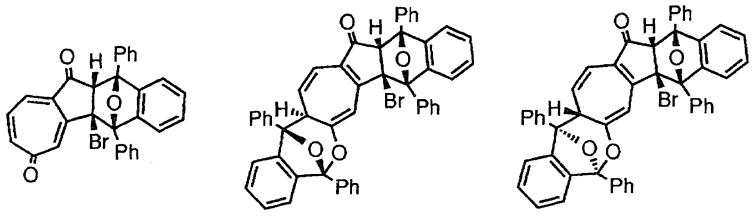
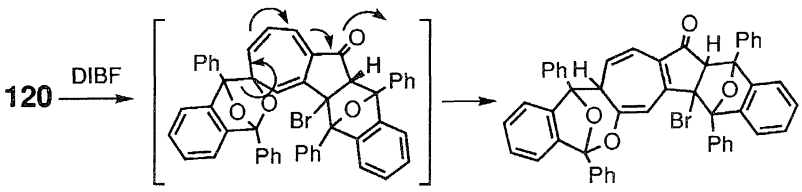


Fig. 8. X-Ray crystal structure of compound **243**.



242 **243** **244**

Chart 14.



Scheme 39.

^{13}C NMR spectral comparison with those of cycloadducts from 3-bromo-1,7-azulenequinone (**121**) elucidated the full stereochemistry. Unlike **249**, both **251** and **252** were inert to cycloreversion.

Isobenzofuran. The thermal cycloaddition of isobenzofuran (IBF) to tropone was previously known to give [2+4]

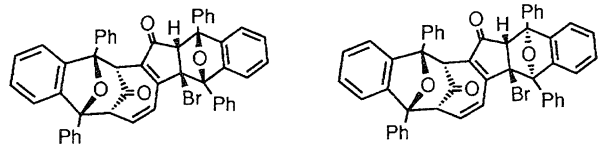


Chart 15.

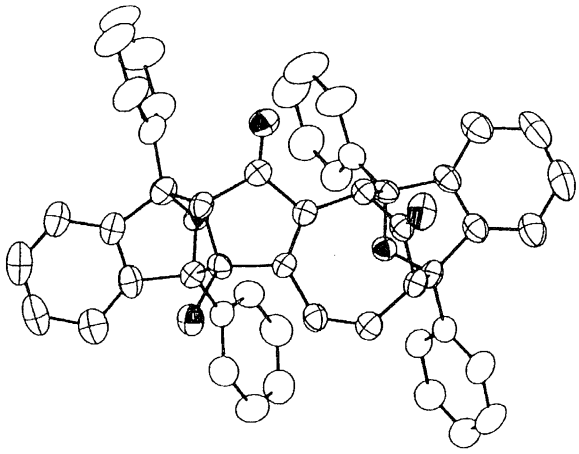
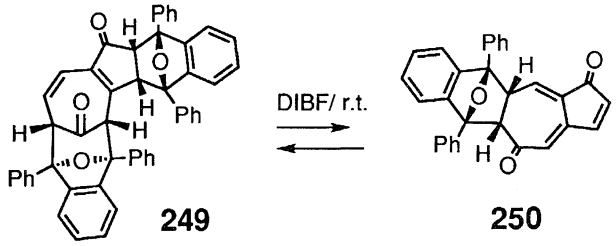


Fig. 9. X-Ray crystal structure of compound **248**.



Scheme 40.

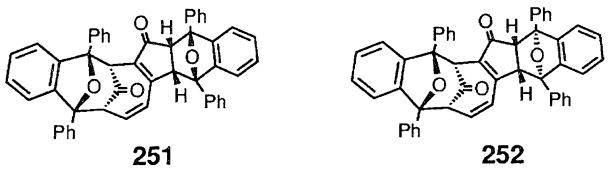


Chart 16.

cycloadducts.[40a] The reaction of bromoazulenequinones with IBF[47] formed the [2+4]–[6+4] cycloadducts, but no [2+4] cycloadduct involving the troponic carbonyl group. Thus, bromoazulenequinones behaved differently from IBF and DIBF; **120** and IBF gave four products, the 1 : 2-[2+4] –[6+4] cycloadducts (**253**, **254**, and **255**) and a 1 : 3-cycloadduct (**256**). From the coupling sequences, **253** was shown to be an *endo*-[2+4]–*exo*-[6+4] product, and a *syn-anti*-relationship was confirmed by an X-ray structure analysis; an ORTEP diagram revealed the *anti-endo*-[2+4]–*exo*-[6+4] structure, as shown in Fig. 10.

The others, **254** and **255**, were *syn*- and *anti-exo*-[2+4] –*exo*-[6+4] products. The remaining product, **256**, was a [2+4]–[6+2]–[2+4] product (Chart 17).

The reaction of IBF with **121** at 130 °C in a chlorobenzene solution gave two products (**257** and **258**), the structures of which were shown to be stereoisomeric 1 : 2-*endo*-[2+4] –*exo*-[6+4] cycloadducts (Chart 18).

Similarly, IBF afforded two stereoisomeric [2+4]–[6+4] cycloadducts (**259** and **260**) with **77**, and four [2+4]–[6+4] cycloadducts (**261**—**264**) with **78**. These structures were firmly established by NMR spectral analyses (Chart 19).

C. Photodimerization. As is described above, azulenequinones and bromoazulenequinones revealed remarkably different features in the thermal cycloaddition reactions. It would therefore be worth investigating the photochemical cycloadditions from a comparative viewpoint. These bromoazulenequinones are tropone derivatives. The photochemical reactions of tropones are known to give several photocyclodimers under various conditions, whereas the parent tropone is known to cause fragmentation to benzene and carbon monoxide in inert solvents[46] and the formation of photodimers are predominant in acidic or polar media.[48] In addition, a recent study revealed a new mode of photoisomerizations

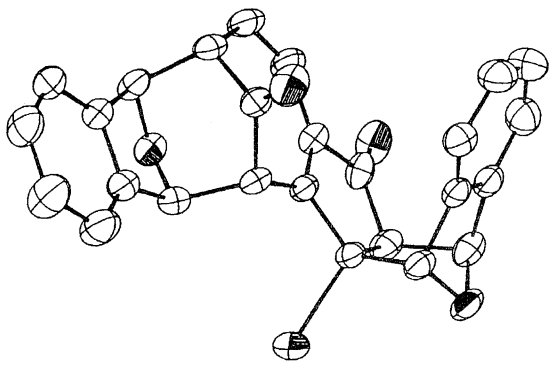


Fig. 10. X-Ray crystal structure of compound **253**.

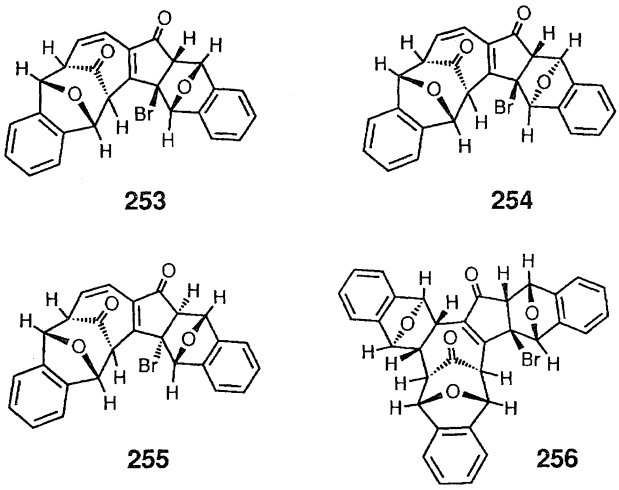


Chart 17.

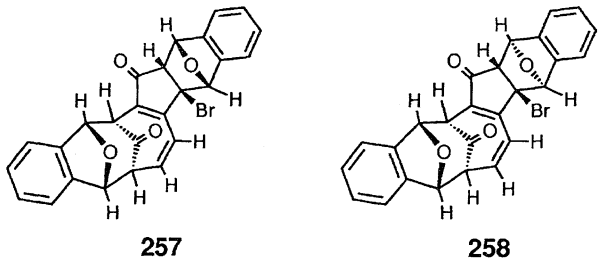


Chart 18.

and photocycloadditions under 9,10-dicyanoanthracene-sensitized conditions.[49]

The irradiation of **120** in a benzene solution by means of an Hg lamp through a Pyrex glass filter gave a single product (**265**).[50] Its ^{1}H NMR spectrum showed five proton signals on the sp^2-carbons and five proton signals on the sp^3-carbons, indicating that the product is a heptacarbocyclic derivative. An analysis of the coupling sequence of the ^{1}H NMR spectrum led to structure **265**, formed by an intramolecular [2+4] cyclization with the initially formed *endo*-[6+6] cyclodimer (or *endo*-[2+2] cyclodimer).

A similar irradiation of **121** in benzene afforded a single product (**266**), a regioisomer of **265** (Chart 20).

For the formation of **265** and **266**, two probable pathways are considered: a) an *endo*-[6+6] cycloaddition (to **E**) followed by an intramolecular [4+2] process, or b) an *endo*-[2+2] cycloaddition (to **F**) followed by an intramolecular [4+2] process. However, since **E** and **F** are mutually convertible via a [5,5] sigmatropy, **E**, a highly reactive cyclopentadienone derivative, and **F** result in the same Diels–Alder cycloaddition to afford **265** and **266**, respectively.

Previously, no *syn*-[6+6] cycloaddition process had been observed in the photochemical reactions of any tropone derivatives (Scheme 41).

In conclusion, the cycloaddition reactions of azulenequinones and bromoazulenequinones were quite sensitive to electronic and stereochemical factors, and were certainly different from those of the monocyclic tropone derivatives. In other words, azulenequinones and bromoazulenequinones are not simply the perturbed tropone derivatives.

Analogues of Azulenequinone

A. Methide Obtained from Guaiazulene. As already described, 5-isopropylidene-3,8-dimethyl-1(5*H*)-azulenone (**48**) was obtained from [5,5′-biguaiazulene]-3,3′(5*H*,5*H*′)-dione (**45**) by autoxidation in $CHCl_3$ in 30% yield. However,

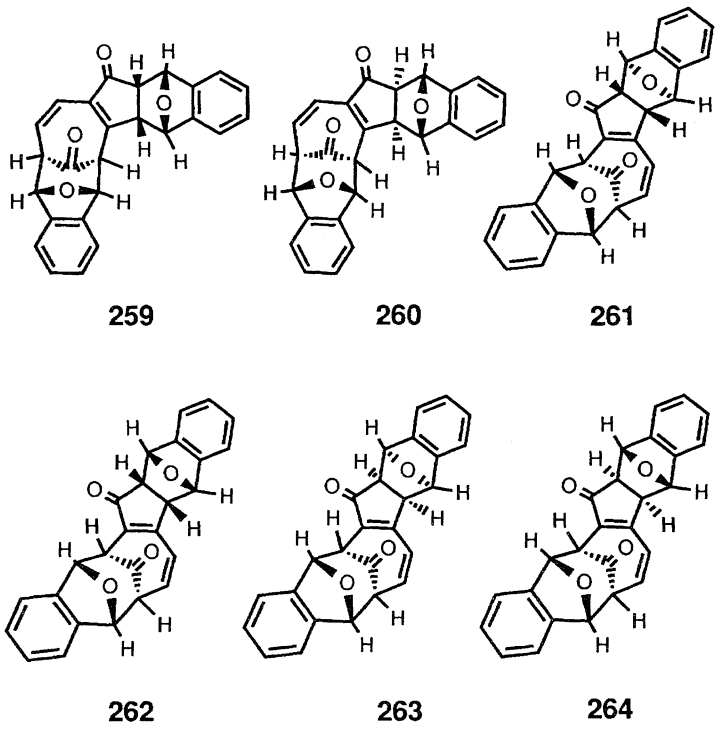


Chart 19.

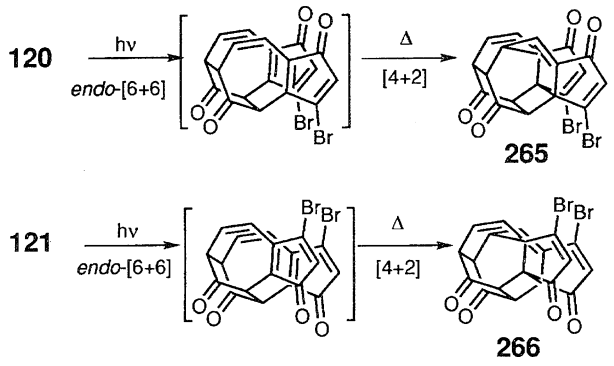


Chart 20.

Matsubara, Yamamoto, Nozoe, and co-workers[11a] obtained nearly quantitative amounts of **48** from **45** in chloroform at 60 °C under a nitrogen atmosphere (anaerobic conditions).[11b]

Interestingly, 6-(3-guaiazulenyl)-3(6*H*)-guaiazulenone (**267**) in chloroform-*d* afforded, instantly and quantitatively, a mixture of guaiazulene-3-*d* (**13a**) and **48** via an intermediate **a** by the action of a trace amount of deuterium chloride[11d] (Scheme 42).

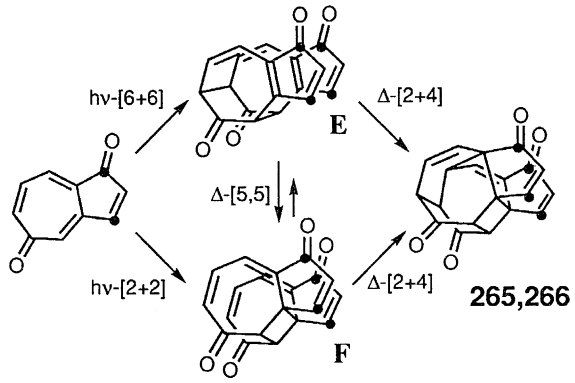
Although **48** was obtained as reddish-orange needles, it was autoxidized instantly in a solution to give various products (**268**—**273** and several other compounds).[12b] Interestingly, when crystals of **48** were left standing at room temperature for several days, they completely changed to 6-formyl-3,7-dimethyl-1-indenone (**269**) in 95.1% yield and its isomer, 5-formyl-3,7-dimethyl-1-indenone (**270**) in 4.9%[11e] (Chart 21).

Although **48** showed no signal in the ESR spectrum under anaerobic conditions, very complex signals were observed under aerobic conditions, which have not been analyzed yet.[12g] At any rate, **48** seems to react as a biradical **48a**. A possible pathway for the formation of several products from **48** is shown in Scheme 43.[12e]

B. Azulenequinone Diazides. Synthesis. As described earlier, an attempted preparation of 2,6-azulenequinones resulted in dimerization at a highly reactive cyclopentadienone moiety.[7] However, masking of these functional groups is thought to be effective in isolating or characterizing the compounds, i.e., a replacement of the C=O by other isoelectronic groups, such as C=C or C=N. Indeed, the C=C stabilization of this system was achieved as early as the 1960s by Hafner et al.[3] The C=N stabilization was also shown by Nozoe et al.[5a] to be effective; 2,6- and 2,4-diazoazulenequinones (**7** and **9**) were prepared by diazotization of the corresponding 2-amino derivatives.[5a—c] Recently, Lin, Huang, Morita, and co-workers[51] dramatically improved the synthetic method of compound **7b** by using CF_3COOH instead of H_2SO_4 upon the diazotization of **6a** and **6b** (Scheme 44).

Structural Studies. The structure of 1,3-dicyano-2-diazo-6(2*H*)-azulenone (**7b**) was established based on the spectra data, and was completely characterized by a single-crystal X-ray analysis, as shown in Fig. 11.[52] Namely, from the characteristic bond lengths, compared with several diazo compounds, benzenoid quinone, and diazonium salts, **7b** should exist as a quinonoidal structure **7b** rather than a diazonioazulenolate ion (**A**, **A′** in Scheme 3) in the solid state.

Reactions. In 1977 Morita and Takase[7b] obtained an 86% yield of **22** (see Scheme 22) by the photochemical decomposition of **7a** in acetic acid with a high-pressure mercury lamp. The thermolysis or photolysis of **7** should form the carbene intermediate **274**, as shown in Scheme 44. The carbene species from **7a** or **7b** should be strongly electrophilic, since the carbene center is conjugated with electron-withdrawing substituents, the tropone carbonyl, ethoxycarbonyl or cyano



Scheme 41.

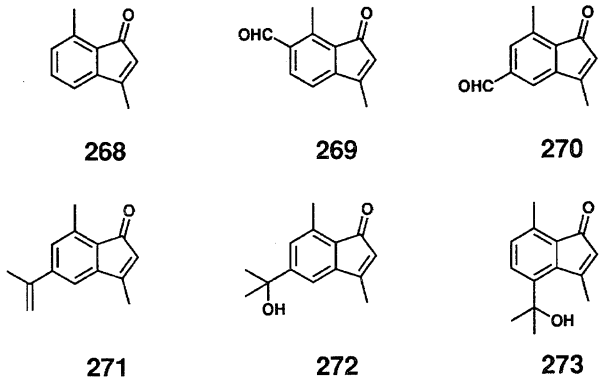
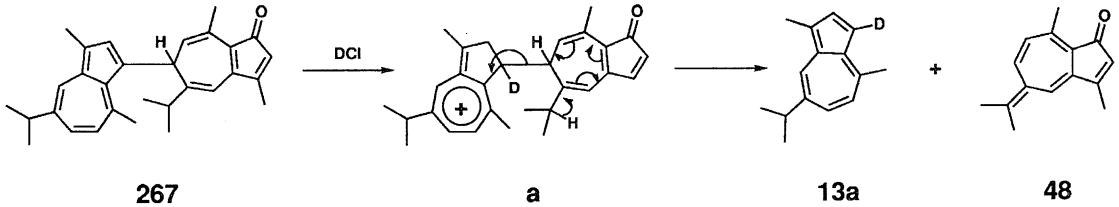
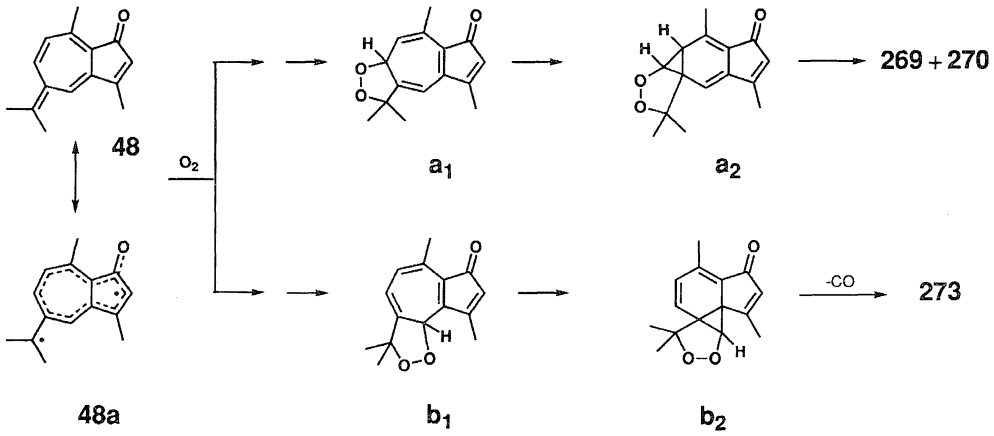


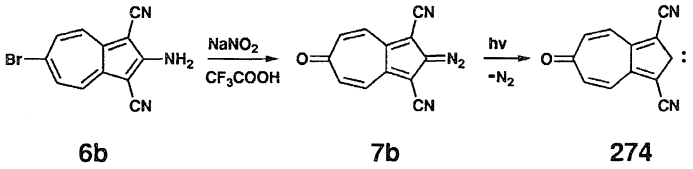
Chart 21.



Scheme 42.



Scheme 43.



Scheme 44.

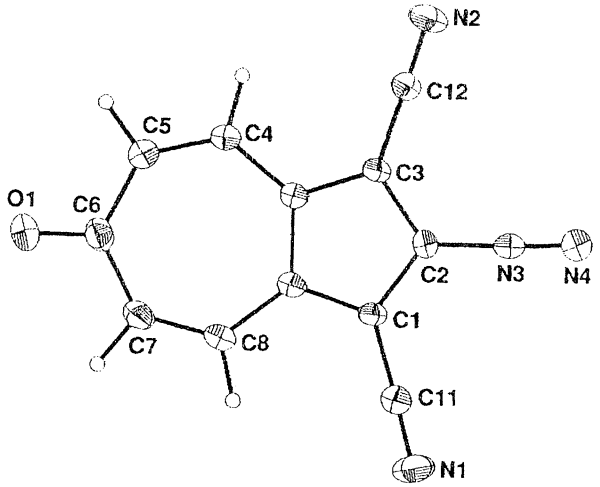


Fig. 11. X-Ray crystal structure of compound **7b**.

groups in the molecules.

Takagi, Nozoe, and co-workers[53] studied the photochemical decomposition of 2-diazo-6(2*H*)-azulenone **7a** in several benzenoid hydrocarbons (**275** and **278**), the result of which is shown in Scheme 45. More interesting was the reaction in 2,6-di-*t*-butylphenol (**278**); the products identified were diethyl 2-(3,5-di-*t*-butyl-4-hydroxyphenyl)-6-hydroxyazulene-1,3-dicarboxylate (**280**) and its isomer **279**. A compound obtained by an attempted dehydrogenation of **280** is believed to be an extended 2,6-azulenequinone derivative (**281**)[53] (Scheme 45).

Nozoe, Lin, and co-workers[54] published an extended study concerning the reaction of 1,3-dicyano-2-diazo-6(2*H*)-azulenone with various protic and aprotic solvents. The photolysis of **7b** in dimethoxyethane (DME), an acyclic ether, in contrast, afforded four compounds produced via different paths; i.e., **283a**, **283b**, **283c**, and **283d**. The major products, **283b** and **283c**, were both 2-(2-methoxyethyl)azulene derivatives. The structure of **283b** was determined by an X-ray diffraction analysis.

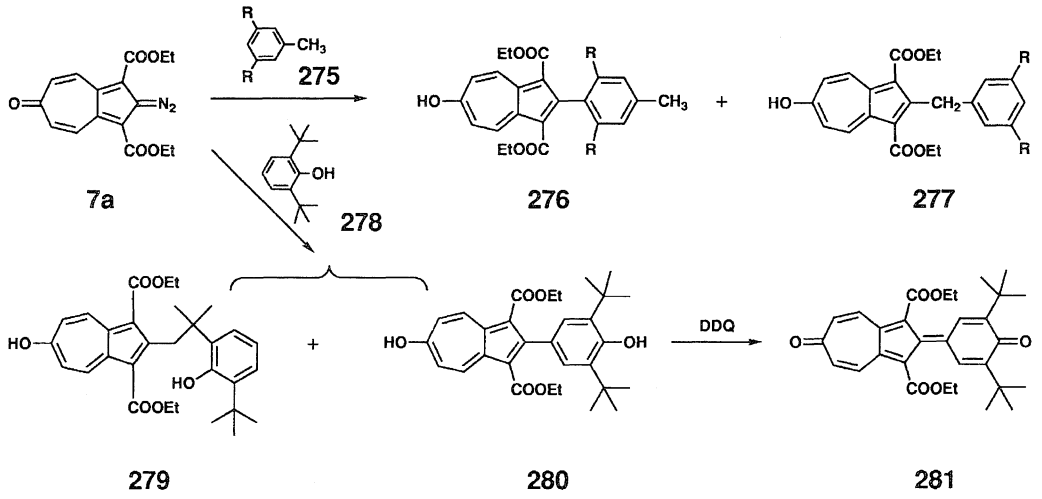
The reactions could be extended to heteroaromatic compounds having no active hydrogen. Thus, **7b** and thiophene gave 2-(1,3-dicyano-6-hydroxy-2-azulenyl)thiophene (**289**), while **7b** and 1-methylpyrrole gave 2-(1,3-dicyano-6-hydroxy-2-azulenyl)-1-methylpyrrole (**288**). Both **289** and **288** are the α-C–H insertion products of the heteroatoms. The photolysis of **7b** in amines, such as morpholine or piperidine, gave similar 2-substituted 6-hydroxyazulene derivatives, 4-(1,3-dicyano-6-hydroxy-2-azulenyl)morpholine (**287**) and **286**. Even with cyclohexane, **7b** gave cyclohexyl derivative (**284**) (Scheme 46).

Crown Ether Formation. The reaction of **7b** in tetrahydrofuran (THF) was particularly interesting; it afforded a macrocyclic oligomeric crown ether **290** in as good as 60% yield. The structure of **290** ($C_{28}H_{36}O_5N_2$) was elucidated on the basis of the ^1H and ^{13}C NMR spectra as well as a mass spectral fragmentation analysis. A possible pathway for the formation of the azulene crown **290** is shown in Scheme 47.

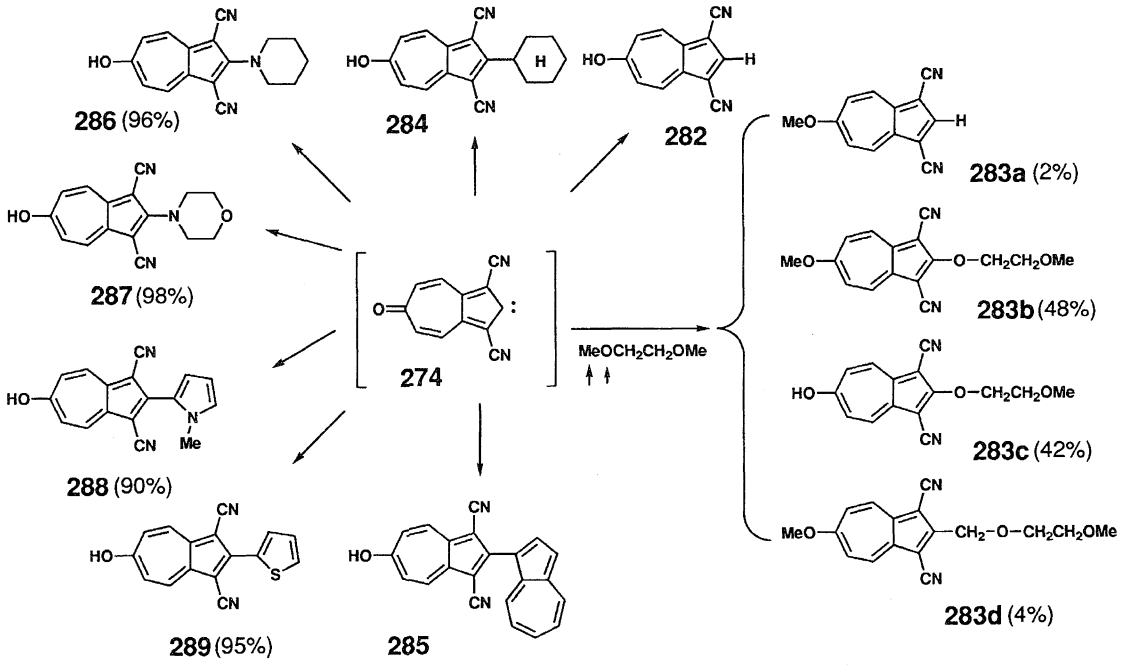
Similarly, two types of 2,4-azulene crown (**292** and **293**) together with 2,4′-diazulenyl ether (**294**) are being studied by Lin, Nozoe, and co-workers. Azoazulenones make very convenient substrates for the synthesis of special types of the azulene crown derivatives (Scheme 48).

Conclusion

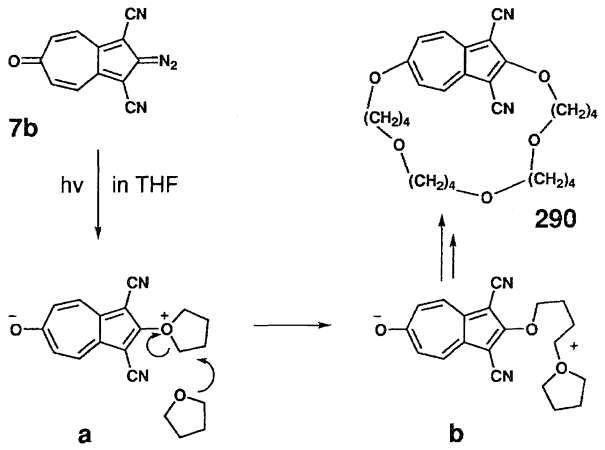
In this article we have presented mainly our results (including incomplete work and some speculative reaction pathways) concerning the field of azulenequinones, which have been rapidly developed in recent years. This is to show the considerable difference in the physical and chem-



Scheme 45.



Scheme 46.

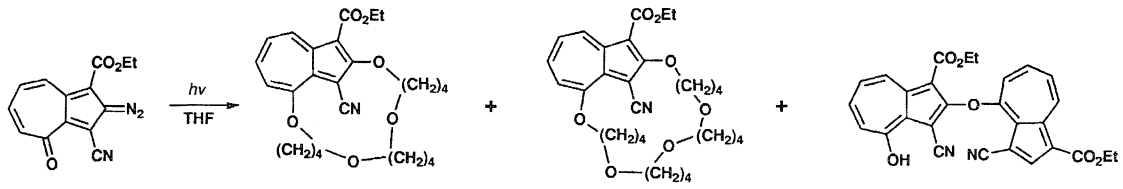


Scheme 47.

ical properties between benzenoid aromatics and azulenes, since such information is thought to be useful for those who are involved in the research of this field.

Our azulenequinone synthesis with bromine oxidation has a wide applicability, and is much superior to the former methods in terms of yield and simple one-pot procedure. However, in view of the further development of applications of azulenequinones, even our present method using bromine may not be suitable for a large-scale synthesis. Since azulenes are generally highly reactive toward oxidation, it is anticipated that a simple autoxidation will be developed by using an appropriate metal-complex catalyst under atmospheric pressure and at room temperature.

Then, by exploiting the azulenequinone research in wider fields of application, such as medicine and semiconductors, it should become possible in the near future to make contri-



291 **292** **293** **294**

Scheme 48.

butions to the welfare of mankind.

Biological Testing. Scott et al. have described that a KB cell cytotoxicity screen test (at the National Cancer Institute, USA) has exhibited significant activity with parent 1,5- and 1, 7- azulenequinones and several di- and triacetoxyazulenes.[1c] Anticarcinogenic activity against PC 388 has been reported by Matsubara[56] for 3,5-guaiazulenequinone; ID50 values (ug/mL) obtained by in vitro screening (Sumitomo Pharmaceuticals Research Center, Osaka) was approximately 1/10 that of adriamycin. Nozoe and Wakabayashi in collaboration with Hwu (Institute of Chemistry, Academia Sinica, Taiwan) have been investigating novel photo-induced DNA-cleavaging test,[57] as well as antibiotic and in vivo antitumor screening against mouse (Sankyo Co., Tokyo); although few significant results have been found so far, an interesting result from this cooperative work is highly anticipated in the near future.

The work on azulenequinone research was initiated about ten years ago by one of the authors (T.N.) in collaboration with Professors Y. Matsubara (Kinki Univ.), H. Yamamoto (Okayama Univ.) and S. Ishikawa (Josai Univ.), then later with Y.-S. Lin (President, Tamkang Univ.) and P.-W. Yang (National Taiwan Univ.), and recently with T.-S. Lin (President, Tatung College of Technology), J. Tsunetsugu (Saitama Univ.), M. Yasunami (Nihon Univ.), K. Fujimori (Shinshu Univ.) and co-workers of these groups. The measurement of the redox potentials and the X-ray analysis were made by Professor T. Miyashi, Drs. T. Suzuki and C. Kabuto (Tohoku Univ.). We wish to express our sincere thanks to all of those collaborators for their devoted work.

We are also very grateful to Professor K. Hafner (T. H. Darmstadt) for the generous gift of a large amount of azulene and to Dr. K. Kohara (Konan Kako Co.) for a supply of guaiazulene, without which this work would not have been realized. Thanks are due professors I. Murata (Fukui Tech. Univ.) and H. Yamamoto (Okayama Univ.) for helpful advice and Dr. T. Kurihara (Josai Univ.) for preparing the figures of this manuscript. Finally, one of the authors (T.N.) wishes to express his deep appreciation to Kao Corporation for its continuing support for his study for the sake of the promotion of basic chemistry, and to the Japan Academy for its continuous financial support.

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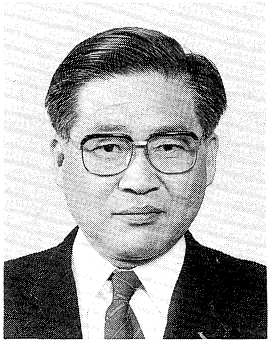
Tetsuo Nozoe was born in Sendai, Japan, on May 16, 1902. He graduated from Tohoku Imperial University in Sendai in 1926 and became research assistant (1926—29) at Government General's laboratories in Taihoku, Taiwan (Japan). He was appointed assistant professor (1929) at the newly established Taihoku Imperial University. After receiving D.Sc. degree from Osaka Imperial University in 1936, he was promoted to professor in 1937. After the World War II he held a joint appointment as professor at National Taiwan University (R.O.C.). He repatriated to Japan in 1948, and was appointed professor of organic chemistry at Tohoku University, Sendai, in the same year. In 1966, he became emeritus professor of Tohoku University.

His research interests have been in natural products chemistry (essential oils, saponins, and wool wax), in particular, in studies of hinokitiol, which he found in 1936 and recognized to be a new type of 7-membered aromatic compound around 1942. Since the end of the war, he has continued the study of a new area of tropylium compounds (troponoids and azulenes), and even now he is being engaged in broadening this area.

He received many awards and honors: Majima Award of The Chemical Society of Japan (1944), Asahi Cultural Award (1952), Japan Academy Award (1953), Order of Cultural Merit (1958), August Wilhelm von Hofmann Memorial Medal of German Chemical Society (1981), and 1st Grand Prize of The Society of Synthetic Organic Chemistry, Japan (1984). He was awarded memberships of The Royal Academy of Science of Sweden (1972), Japan Academy (1978), and honorary membership of The Swiss Chemical Society (1978). He was also awarded honorary citizenships of Sendai (1959) and Taipei (1982). He served as a founding chairman of the first IUPAC-sponsored International Symposium on Novel Aromatic compounds in Sendai (1970), which held its 8th international meeting in Braunshweig, Germany (1995).

Suddenly, he passed away in April 4, 1996.



Hitoshi Takeshita was born in Shirakawa, Fukushima Prefecture, in 1932. He graduated from Tohoku Univ. in 1955, and got B.Sc. degree under the guidance of Prof. Tetsuo Nozoe. He was given D.Sc. degree in 1960 (Prof. Tetsuo Nozoe). Then, he was a Post Doctoral research student supported by Japan Society of Promotion of Science from 1960 to 1961 (also under the guidance of Prof. Tetsuo Nozoe).

He had a career of post doctoral fellow at Univ. of Western Ontario (1961—1963, Prof. Paul de Mayo) and at New York Botanical Garden (1963—1964, Dr. Marjorie Anchel). He was appointed as a lecturer of Tohoku University (Fac. Science) in 1965, and promoted to an assistant professor of Tohoku Univ. (Fac. Science) in 1966.

In 1972, he moved to Kyushu Univ. (Research Inst. Industrial Science, which renamed as Inst. Advanced Material Study in 1982) as a professor. He was the director of the Institute where he belongs (1987—1989), and chairman of Kyushu Division of Chemical Society of Japan (1992).

His research interests have been the chemistries of natural products and novel aromatic compounds particularly from the synthetic aspects.