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# RECENT ADVANCES IN THE CHEMISTRY OF BRIDGED ANNULENES

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Abstract – Two major – complementary – synthetic approaches to bridged [4n+2]annulenes with a naphthalene or an acene perimeter, which allow the chemistry of these annulenes to be explored on a broad basis, have been developed. The first one, embracing the synthesis of a great variety of bridged [10]- and [14]annulenes, is founded on the Birch reduction products of naphthalene and anthracene, respectively, as starting materials. The second, more recent one, takes advantage of the synthon cycloheptatriene-1,6-dicarboxaldehyde – to be regarded as homo-phthalaldehyde – that has now become available on a potentially technical scale from cycloheptatriene. It is the virtue of cycloheptatriene-1,6-dicarboxaldehyde that it provides access to homologous series of $CH_2$-bridged [10]-, [14]-, [18]-, and lately even [22]annulenes by a "building-block" strategy.

## INTRODUCTION

In 1964-65 the bridged [10]annulenes (1) 1,6-methano[10]annulene 1(X=$CH_2$) (2), 1,6-oxido-[10]annulene 1(X=O) (3), and 1,6-imino[10]annulene 1(X=NH) (4) have yielded to synthesis in the Cologne laboratory. Complying with Hückel's rule electronically and – to a good approximation – also sterically, these annulenes, in striking contrast to the parent [10]-annulenes (with all-cis- and mono-trans-configuration, respectively) isolated and characterized years later by S. Masamune (5), were found to qualify as aromatic molecules in both physical and chemical respects.

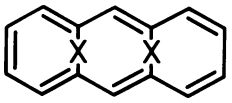
1

X=$CH_2$,O,NH

The structural relationship existing between the bridged [10]annulenes 1 and naphthalene suggested the idea that the imaginary series of potentially aromatic bridged [4n+2]annulenes 2, 3, 4, and so on, corresponding to the series of classical aromatic hydrocarbons, the acenes, could actually be developed experimentally.

It is an important feature of these bridged [4n+2]annulenes that they give rise to geometrical isomerism. As an inspection of molecular models of 2 and its homologues reveals, only the [4n+2]annulenes with the bridges in a syn- or all-syn-arrangement and with bridges not too demanding in space possess $C_{(4n+2)}$-perimeters flattened out sufficiently to allow delocalization of the π-electron system and hence aromaticity of the respective molecules (6).

In our quest to translate this concept into real molecules we have been able up to now to devise two expedient complementary synthetic approaches to bridged annulenes with a naphthalene or an anthracene perimeter.



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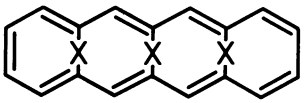

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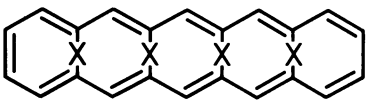


4

X=$CH_2$,O,NH

The first one, embracing the synthesis of a great variety of bridged [10]- and [14]annulenes is based on 1,4,5,8-tetrahydronaphthalene and 1,4,5,8,9,10-hexahydroanthracene, respectively, as starting materials. The second, more recent one, takes advantage of the synthon cycloheptatriene-1,6-dicarboxaldehyde 5 that has become readily available from cycloheptatriene (7).


5

It is the virtue of 5 that it provides access to homologous series of $CH_2$-bridged [10]-, [14]-, [18]-, and even [22]annulenes by a "building-block" strategy. The dialdehyde 5, moreover, promises to open up an entry into the realm of bridged aza[4n+2]annulenes through appropriate methods of annelation.

The fact that the bridged [10]annulenes and many of the bridged [14]annulenes (syn-series), apart from being distinguished by remarkable stability, can now be prepared in sizable quantities, has rendered these annulenes rewarding objects for detailed chemical exploration.

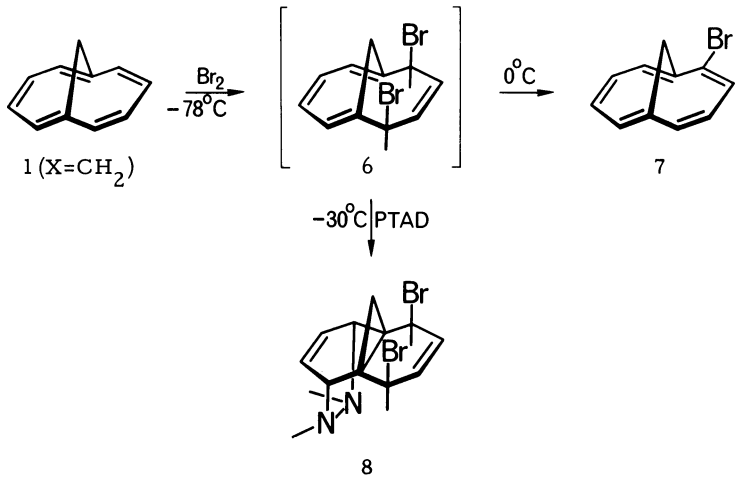
## BRIDGED [10]ANNULENES

In the first part of this lecture I would like to focus your attention on some new aspects of the chemistry of bridged [10]annulenes, specifically of the parent 1,6-methano[10]annulene 1(X=$CH_2$), of 11-oxo-1,6-methano[10]annulene 15, and of the heterocycle 1,6-imino[10]-annulene 1(X=NH).

### 1,6-Methano[10]annulene 1(X=$CH_2$)

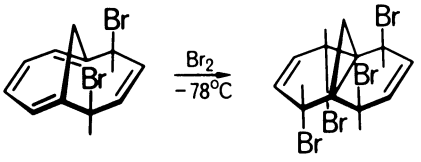
By analogy to the chemistry of benzene, one of the key chemical reactions of 1,6-methano-[10]annulene 1(X=$CH_2$) is bromination. As has been shown in the initial studies of the reaction of 1(X=$CH_2$) with electrophiles (1a), treatment of the hydrocarbon with one mole of bromine at room temperature regioselectively affords one of the two possible substitution products, namely 2-bromo-1,6-methano[10]annulene 7 (8,9). That the 2-position of 1(X=$CH_2$) is the preferred site of attack by bromine and other electrophiles, has subsequently been rationalized by extended Hückel- and by CNDO-calculations. Under proper conditions, bromination of 1(X=$CH_2$), moreover, leads to the 2,7-, 2,10-, and 2,5-dibromo-1,6-methano-[10]annulenes and to 2,5,7,10-tetrabromo-1,6-methano[10]annulene (10). Both 7 and the various more highly brominated 1,6-methano[10]annulenes lend themselves to synthetically useful transformations by conventional chemical methods and thus constitute the backbone, so to speak, of 1,6-methano[10]annulene chemistry (11).

The substitution product 7 is assumed to be formed by an addition-elimination mechanism since bromination of 1(X=$CH_2$) at -78°C affords the non-isolable dibromo adduct 6 (or its stereoisomer with inverse configuration of the bromine atoms), which readily yields 7 when the reaction mixture is warmed to 0°C. Unfortunately, it was not possible to elucidate the complete stereochemistry of the dibromo adduct by spectroscopic methods. Therefore, the intriguing stereochemical question of whether bromine attacks 1(X=$CH_2$) from the syn- or anti-position with respect to the $CH_2$-bridge remained.



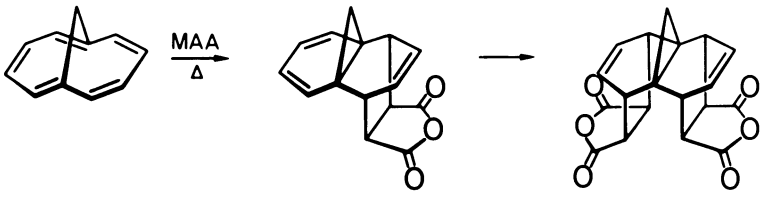

1 (X=$CH_2$) 6 7 8

We have now been able to trap the dibromo adduct at -30°C by the potent dienophile 4-phenyl-1,2,4-triazoline-3,5-dione with formation of a Diels-Alder adduct which could be shown by X-ray analysis to possess structure 8 (12). From this result it follows that the dibromo adduct of 1(X=$CH_2$) is the stereoisomer 6 and that, accordingly, the attack of bromine on 1(X=$CH_2$) occurs from the more hindered syn-position. A theoretical study aimed at clarifying the cause of this surprising stereochemistry of the bromination of 1(X=$CH_2$) is currently being carried out by Professor R. Gleiter.




6 9

An X-ray investigation also served to reveal the hitherto undetermined configuration of the tetrabromo adduct formed on reaction of 1(X=$CH_2$) with two moles of bromine at -78°C as the only isolable product. As the tetrabromide turned out to be 9, it is evident that 6 is approached by bromine from the anti-position (12).

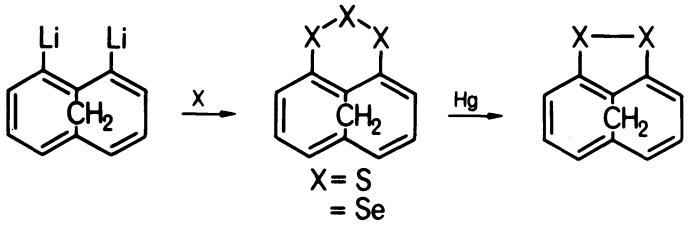



1 (X=$CH_2$) 10 11

The syn-attack of bromine on 1(X=$CH_2$) and on 1(X=O) (12) is all the more remarkable as cycloadditions to these bridged [10]annulenes - studied extensively in collaboration with Professor D. Ginsburg (13) in connection with his concept of secondary orbital-overlap control during Diels-Alder reactions of propellanes (14) - are found to occur from the anti-position exclusively. Thus, maleic anhydride adds to 1(X=$CH_2$) to give 10 which on further reaction with the dienophile affords 11. The stereochemistry of both of these adducts follows from an X-ray analysis of the bis-adduct performed by the Haifa group (15).

The chemical versatility of the aforementioned bromo substitution products of 1(X=$CH_2$) may be exemplified by the conversion of 2,10-dibromo-1,6-methano[10]annulene into com-

pounds 14(X=S) and 14(X=Se) having the peri-positions linked by bridges consisting of two chalcogen atoms (16). The disulfide 14(X=S) is obtained when 12, readily available from the dibromide and butyl lithium, is treated successively with sulfur and mercury. Replacement of sulfur by selenium in this reaction sequence leads to the diselenide 14(X=Se). Interestingly, the reactions of 12 with the chalcogens mentioned afford the trisulfide 13(X=S) and the triselenide 13(X=Se), respectively, as primary products which are stable enough to be isolated.

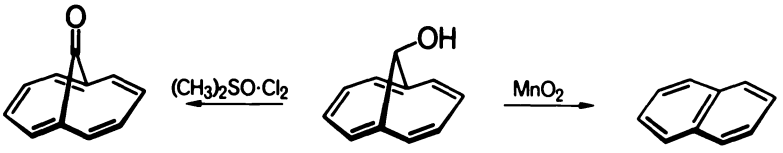



12 13 14

The syntheses of 14(X=S) and 14(X=Se) have been stimulated by the report of J. Meinwald (17) that naphtho[1,8-c,d]-1,2-dithiole and naphtho[1,8-c,d]-1,2-diselenole are good electron donors, capable of forming stable, presumably one-dimensional charge transfer complexes with 7,7,8,8-tetracyanoquinodimethane (TCNQ). Although, 14(X=S) and 14(X=Se) are prevented from forming one-dimensional charge transfer complexes due to the presence of the $CH_2$-bridge, it will be interesting to find out how these 1,6-methano[10]annulenes behave towards electron acceptors such as TCNQ.

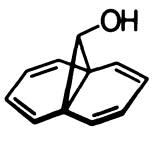
11-Oxo-1,6-methano[10]annulene 15

Let me now present some recent observations on the fascinating 11-oxo-1,6-methano[10]-annulene 15, a molecule synthesized originally and most elegantly by S. Itô (18) from the (6+4)-adduct of butadiene and tropone. At the Cologne laboratory the report of the Japanese group was at first met with disbelief as our previous efforts to prepare 15 by oxidation of the alcohol 16 with manganese dioxide, Jones reagent, or lead tetraacetate had always resulted in the formation of naphthalene in excellent yield, suggesting the keto compound 15 to undergo decarbonylation very readily (1a).




15 16

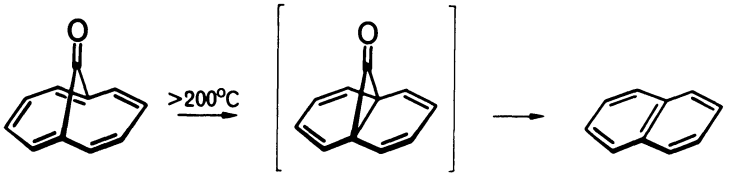
The apparent discrepancy between the results of Itô and ourselves disappeared when we found that the oxidation of 16 with the aforementioned reagents to naphthalene does not involve 15 as an intermediate. In all likelihood, this oxidation of 16 occurs via the cyclopropanol derivative 17, the tricyclo[4.4.1.$0^{1,6}$]undeca-2,4,7,9-tetraene valence tautomer of 16. As is well documented, cyclopropanols show some chemical resemblance to phenols in that they experience radical abstraction of the OH-hydrogen atom with concomitant rupture of the cyclopropane ring on treatment with metal ions, such as $Fe^{III}$ or $Cu^{II}$ (19). Rupture of the cyclopropane ring of 17 in this fashion can easily be envisioned to provide a pathway for loss of the carbon bridge. If such a mechanism applies, one would expect that




17

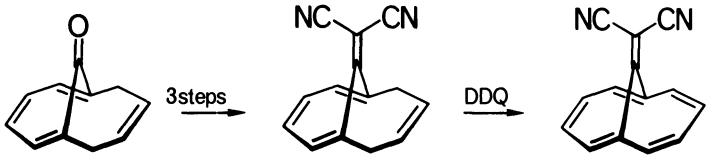
oxidation of 16 by reagents other than those based on multivalent manganese, chromium, or lead would yield 15. Indeed, both the Pfitzner-Moffat reagent and Corey's dimethylsulfoxide complex smoothly convert 16 into 15, the formation of naphthalene being suppressed completely (20).

One of the most remarkable properties of 15 is its thermal stability (18). It is only on heating of 15 to 200°C that the anticipated fragmentation of the molecule into naphthalene and carbon monoxide does take place. This stability is presumably due to the reluctance of 15 to isomerize to its cyclopropanone-type valence tautomer 18 which is invoked as an intermediate in the fragmentation.




15 18

From the synthetic point of view, 11-oxo-1,6-methano[10]annulene 15 seemed to be a key compound among the 1,6-methano[10]annulenes since it promised access to many other bridge substituted 1,6-methano[10]annulenes through nucleophilic additions at the carbonyl group. Thus, olefination reactions of 15 should provide 11-methylene-1,6-methano[10]annulenes (1a), such as the dicyano compound 21, which command interest as possible sources of vinylidene carbenes and for other reasons. Contrary to expectation, however, the carbonyl group of 15 has not allowed the hoped for synthetic exploitation of the compound. Most of the nucleophiles with which 15 was treated either failed to react or led to adducts which underwent spontaneous fragmentation to naphthalene and, supposedly, carbenes.

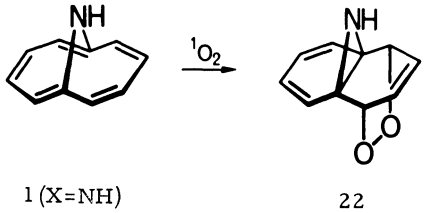



19 20 21

In search of an alternative route to 11-methylene-1,6-methano[10]annulenes with substituents at the bridge double bond, it recently occurred to us that 2,5-dihydro-11-oxo-1,6-methano[10]annulene 19, available from 11,11-dibromo-tricyclo[4.4.1.$0^{1,6}$]undeca-3,8-diene by a four-step process, should be amenable to olefination. This scheme has since led to 20 which could be dehydrogenated by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to give 21 as the first 11-methylene-1,6-methano[10]annulene bearing substituents at the 12-position (21). Further work along this line is in progress.

1,6-Imino[10]annulene 1(X=NH)

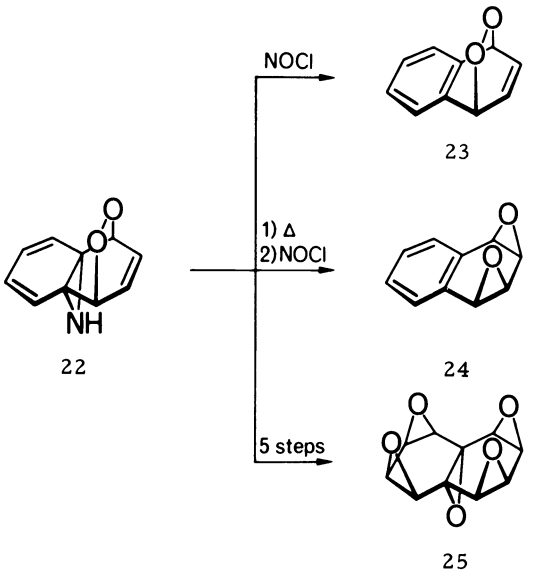
During the last few years interesting new chemistry has also emerged from the heterocycle 1,6-imino[10]annulene 1(X=NH), one of the earliest members of the ever increasing family



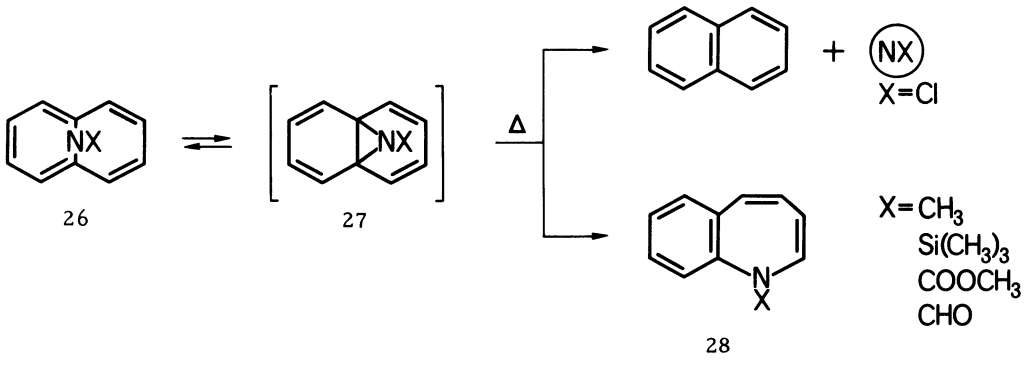

1(X=NH) 22

of bridged [10]annulenes. Similar to the 1,6-methano[10]annulenes, which in some cases were found to be sources of benzocyclopropenes and/or carbenes, 1(X=NH) has proved to be a most valuable starting material for the synthesis of novel molecules no longer related to bridged annulenes.

Thus, photooxidation of 1(X=NH) with singlet oxygen, smoothly affording the 1,4-endoperoxide 22 with a benzene imine structural moiety, has linked the chemistry of bridged [10]-annulenes with arene oxide chemistry, which has been an area of research in this laboratory since our discovery of the benzene oxide-oxepin system (22). As we have shown recently, 22 can straightforwardly be converted by standard methods into naphthalene-1,4-endoperoxide 23 (23) - incidentally, a new source of singlet oxygen - and into a series of naphthalene polyoxides including syn-1,2:3,4-naphthalene dioxide 24 (24) and the stereoisomer 25 of the rather exotic naphthalene pentoxide 25 (25). Compound 25 is distinguished by the unusual structural feature of possessing two fused "planar cyclohexane rings".

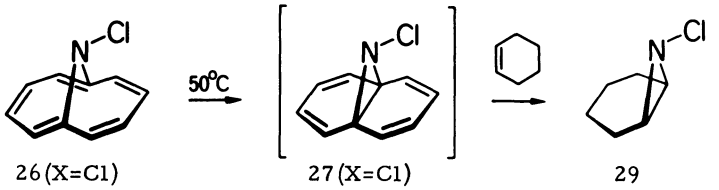



Some additional synthetically useful transformations were encountered in the thermolysis of N-substituted 1,6-imino[10]annulenes 26. This study was undertaken because we reasoned that the thermal fate of such 1,6-imino[10]annulenes should be strongly dependent on the nature of the substituent on nitrogen. There is ample analogy (1a) to assume that the thermolysis of 26 will proceed through the benzene imine type valence tautomers 27 as transient intermediates. These species may either undergo fragmentation into a nitrene and naphthalene or they may experience sort of a Berson-Willcott rearrangement with formation of the as yet hardly known 1H-1-benzazepines 28 (26).



As it turned out, 1H-1-benzazepines are the predominant or exclusive products of thermolysis when X is $CH_3$, $Si(CH_3)_3$, $COOCH_3$, and CHO, whereas nitrene extrusion is observed when X is Cl (27).

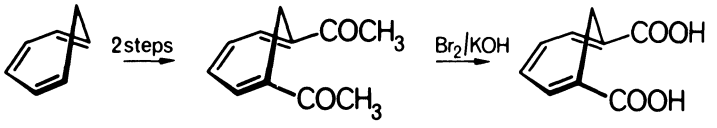
Evidence for the formation of chloronitrene on thermolysis of N-chloro-1,6-imino[10]annulene 26(X=Cl) is based on trapping experiments. When the thermolysis of 26(X=Cl), which takes place at the surprisingly low temperature of 50°C, is carried out in the presence of cyclohexene, the N-chloroaziridine 29 is obtained in 25 % yield. The ease with which the thermolysis of 26(X=Cl) occurs seems to indicate that the still relatively unexplored halonitrenes may derive special stabilization by halogen as is the case with the halocarbenes.



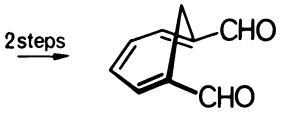

26(X=Cl) 27(X=Cl) 29

1,6-Methano[10]annulene 1(X=$CH_2$) from cycloheptatriene-1,6-dicarboxaldehyde 5

In the last few years the synthesis of $CH_2$-bridged [10]annulenes has received added momentum by the introduction of a new synthon, namely cycloheptatriene-1,6-dicarboxaldehyde 5 (7), which, as already mentioned, nicely complements the 1,4,5,8-tetrahydronaphthalene synthon. This dialdehyde has recently become readily accessible due to the discovery that cycloheptatriene 30, under proper conditions, can be acetylated at the termini of the double bond system to give 1,6-diacetylcycloheptatriene 31. The subsequent conversion of the diacetyl compound into the dialdehyde by way of cycloheptatriene-1,6-dicarboxylic acid 32 (28) is achieved effectively by conventional procedures.




30 31 32

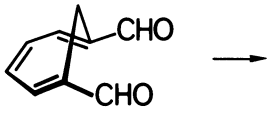



5

The synthetic usefulness of cycloheptatriene-1,6-dicarboxaldehyde 5 becomes best apparent if we regard it as "homo-phthalaldehyde". Similar to the classical phthalaldehyde, 5 especially invites chemical transformations leading to annelations.

As regards the conversion of 5 to 1,6-methano[10]annulene 1(X=$CH_2$), we have been able to devise no less than three methods of annelation, all of which are based on 10π-electrocyclic processes. The method of choice consists of the following steps: 1) successive olefination of 5 with the Wittig reagents methylene(triphenyl)phosphorane and chloromethylene(triphenyl)-phosphorane to give 33 and 2) heating of 33 in dimethylformamide to yield 1(X=$CH_2$) by "cyclodehydrohalogenation", i.e., by a 10π-electrocyclic process combined with elimination of hydrogen chloride from the labile 3,4-dihydro-1,6-methano[10]annulene intermediate 34 (29).

This scheme has since been extended to a general method of synthesis of 3- and 3,4-substituted 1,6-methano[10]annulenes by appropriate variation of the Wittig reagents in the initial two-stage olefination step.

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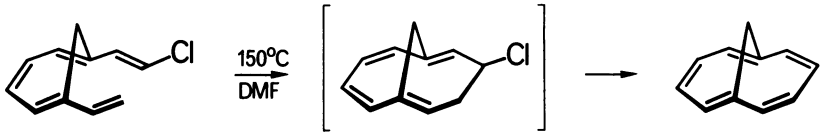
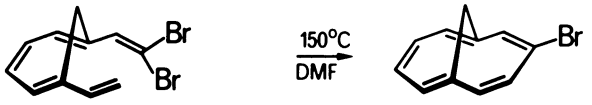



33 34 1 (X=$CH_2$)

As representative examples I would like to mention the smooth preparation of 3-bromo-1,6-methano[10]annulene 36 and of 3,4-dicarbomethoxy-1,6-methano[10]annulene 38, the phthalic ester analogue in the 1,6-methano[10]annulene series, from the respective olefination products of 5, namely 35 and 37 (29).




35 36


37 38

In view of the fact that 1,6-methano[10]annulene on treatment with electrophilic reagents preferentially furnishes 2-substituted 1,6-methano[10]annulenes, the synthesis of 3- and 3,4-substituted 1,6-methano[10]annulenes from 1 (X=$CH_2$) through the above annelation scheme has filled a hitherto existing gap in 1,6-methano[10]annulene chemistry.

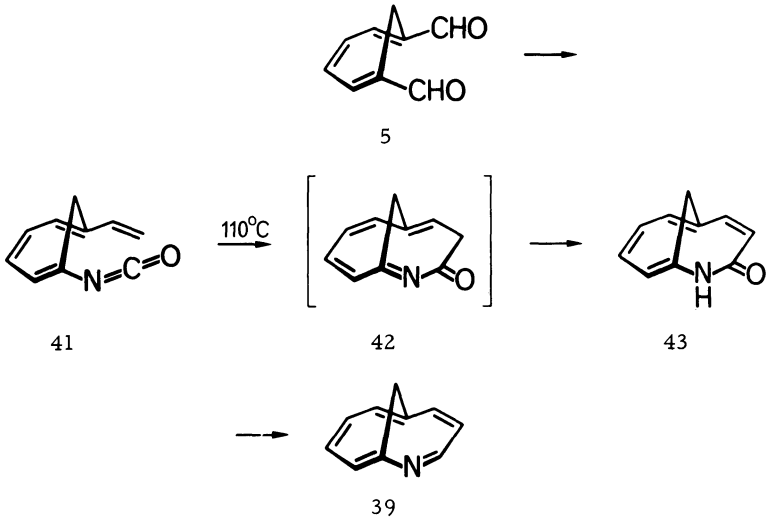
2,7-Methanoaza[10]annulene 39

It is the special virtue of cycloheptatriene-1,6-dicarboxaldehyde 5 that it also should provide an entry to the as yet virtually untouched field of $CH_2$-bridged [10]annulenes containing one or two nitrogen atoms in the peripheral ring, i.e., aza- and diaza[10]annulenes (30). Such novel heterocycles, constituting 10π-analogues of the classical heteroaromatic compounds pyridine, pyrimidine, pyridazine, and pyrazine, respectively, unquestionably attract great interest both for theoretical and for practical reasons.


39 40

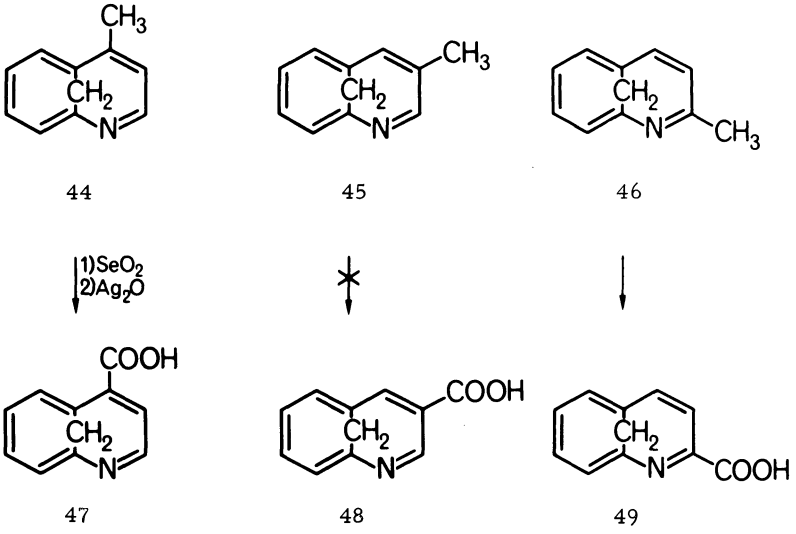
Naturally, it has been one of our main goals in this field to build up the two possible bridged aza[10]annulenes derived from 1,6-methano[10]annulene, i.e., 2,7-methanoaza[10]annulene 39 and 3,8-methanoaza[10]annulene 40. While 40 has so far escaped synthesis (31), 39 could be prepared from 5 by an annelation scheme that features the isocyanate 41 as the key intermediate (32). The supposition that 41 would isomerize thermally by a 10π-electrocyclic process – involving the isocyanate carbon nitrogen double bond – to the azaenone 42, and that 42 would spontaneously undergo a prototropic shift to give the lactam 43 was borne out

by experiment. On heating 41 in toluene, 43 is obtained as the main product. The subsequent transformation of 43 into 39 was best effected via the O-tosylate of 43. 2,7-Methanoaza[10]-annulene thus prepared proved to be a stable aromatic compound.




5 41 42 43 39

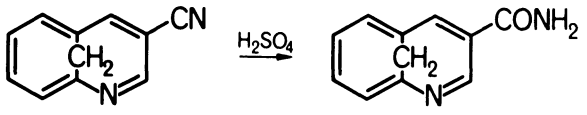
Interestingly, 2,7-methanoaza[10]annulene 39, having a $pk_a$-value of 3.20, is more weakly basic than pyridine or quinoline ($pk_a$ = 5.23 and 4.94, respectively). Despite its low basicity, 39 affords a stable hydrochloride with dry hydrogen chloride in ether, can be alkylated with various methylating agents to give the corresponding salts, and is capable of forming an N-oxide (33) – a 10π-analogue of pyridine oxide – on treatment with peracids.




44 45 46 47 48 49

In order to study the influence of substituents on the basicity of the 2,7-methanoaza[10]annulene system, the methyl compounds 44, 45, and 46 as well as other derivatives of 39 became targets of synthesis. Actually, 44 and 45 could be obtained by application or modification (in the case of 45) of the synthetic scheme leading to the parent 39 (34). The methyl compound 46, the synthesis of which required different methodology, was found to be accessible by treatment of the oxime of 1-acetyl-6-vinylcycloheptatriene with p-toluenesulfonyl chloride and trimethylamine (Beckmann rearrangement with neighbouring group participation of the vinyl double bond) (34). Attesting to the astonishing chemical stability of the 2,7-methanoaza[10]annulene system, 44 and 46 are oxidized to the acids 47 and 49, respectively, by successive treatment with selenium dioxide and silver oxide, whereas 45 remains essen-

tially unchanged under these conditions (34). This, incidentally, is the same reactivity pattern observed in the oxidation of the three methylpyridines.




50 51

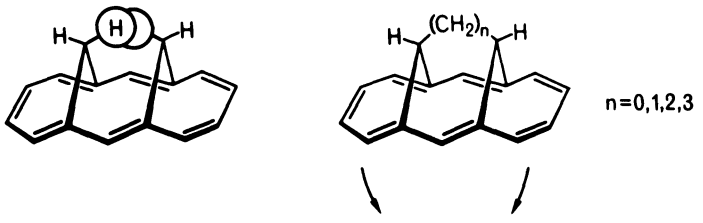
Failure of the methyl compound 45 to undergo oxidation to the acid 48 was somewhat disappointing to us, since the amide 51 of 48, representing a 10π-analogue of nicotine amide, is of obvious biochemical interest as a pyridine nucleotide model. The acid 48 and its amide 51 were therefore approached through the nitrile 50, which, as is the case with 45, is available by a modified version of the scheme of synthesis of 39. While the attempted alkaline hydrolysis of 50 proved difficult, treatment of 50 with 95 % sulfuric acid at room temperature smoothly afforded 51, and this on reaction with 75 % sulfuric acid at 130°C finally gave 48 (35). A collaboration with biochemists has now been initiated in order to find out if molecules of this type exhibit biological activity.

## BRIDGED [14]ANNULENES

### Aromaticity and molecular geometry

After this survey of the recent development of the syntheses and chemistry of bridged [10]annulenes and aza[10]annulenes we shall proceed to the bridged [14]annulenes with an anthracene perimeter, which exist as syn- and anti-stereoisomers. Over the last decade quite a number of such [14]annulenes, representing both stereochemical types, has yielded to synthesis starting from 1,4,5,8,9,10-hexahydroanthracene 56, the Birch reduction product of anthracene (1d, 6).

Unfortunately, the particularly interesting syn-1,6:8,13-bismethano[14]annulene 52, the potentially aromatic next higher homologue of 1,6-methano[10]annulene is not accessible by this approach. However, the systematically bent bridged [14]annulenes 53, derived from 52 by removal of its inner bridge hydrogen atoms (n = 0) or by replacing them by one, two, or three methylene groups, could be prepared from 56 by multistep routes. In addition, anti-1,6:8,13-bismethano[14]annulene, possessing a puckered annulene ring, has been synthesized taking advantage of 56.



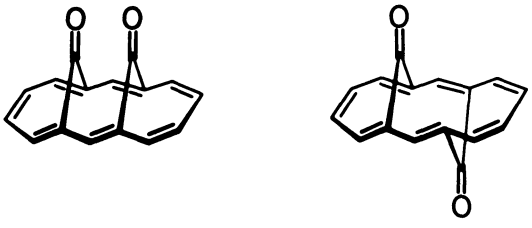

52 53

As the description bent and puckered already indicates, it is an essential geometrical feature of the bridged [14]annulenes with an anthracene perimeter that the shape or conformation of the annulene ring of these molecules is strongly dependent on the steric arrangement as well as on the nature of the bridges. Hence, this type of bridged [14]annulenes seemed to be well suited for the overdue experimental scrutiny of the steric conditions for aromaticity implied in Hückel's rule, i.e., the presence of a planar ring skeleton. The extensive spectroscopic and structural investigations on these annulenes, carried out in collaboration with experts in the respective fields, made it apparent that a [4n+2]annulene is capable of tolerating rather striking deviations from planarity without suffering a significant loss of its π-electron delocalization. A "breakdown" of the π-electron delocalization in such an annulene can, of course, be realized, but requires severe distortions of the annu-

lene ring. Such conditions are met with anti-1,6:8,13-bismethano[14]annulene which accordingly is found to be an olefinic molecule (1d, 6).

15,16-Dioxo-syn- and 15,16-Dioxo-anti-1,6:8,13-bismethano[14]annulene 54 and 55

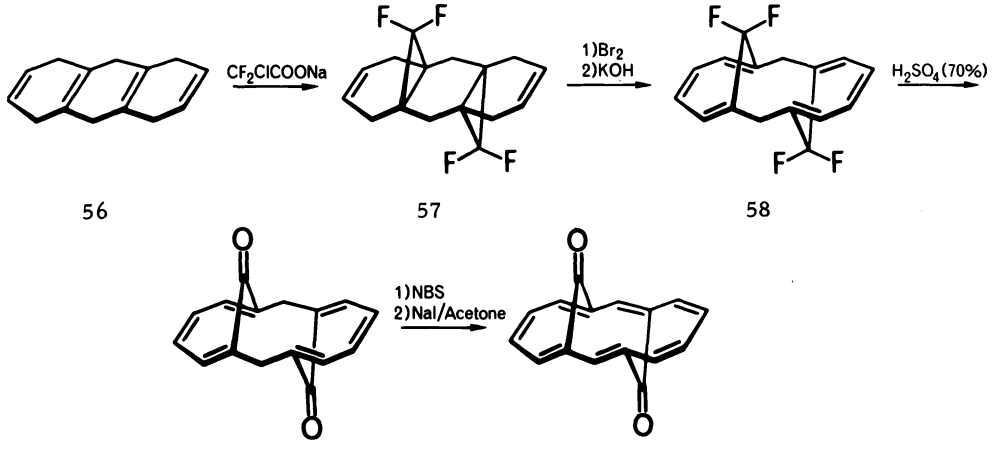
The structural factor governing the properties of the bridged [14]annulenes with an anthracene perimeter most pronouncedly appears to be the steric arrangement of the bridges. Probably, the most telling demonstration of this dependency is provided by the dramatically different spectroscopic and chemical behaviour of the two stereoisomeric [14]annulenes bridged by carbonyl groups, the 15,16-dioxo-syn-1,6:8,13-bismethano[14]annulene 54 and its anti-isomer 55. After many futile previous efforts, both of these molecules have been synthesized recently from 56 (36).



syn anti

54 55

The synthesis of the anti-isomer 55, to be described first, is based on the observation that addition of difluorocarbene – serving as a latent carbonyl group – to the central double bonds of 56 exclusively occurred in an anti-fashion to give 57. Successive treatment of 57 with bromine and potassium hydroxide leads to the $CF_2$-bridged dihydro[14]annulene 58 which could be hydrolysed to the CO-bridged dihydro[14]annulene 59 by 70 % sulfuric acid. Introduction of the final double bond into 59 was effected by the reaction of the compound with two moles of N-bromosuccinimide and subsequent dehalogenation of the bromination products thus formed with sodium iodide in acetone.

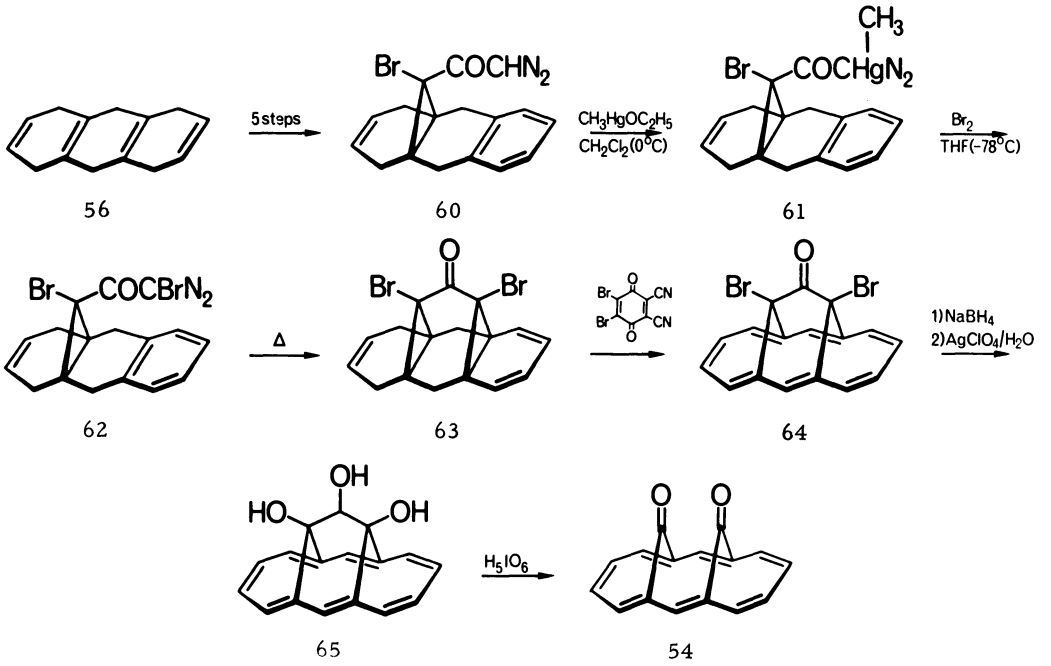



56 57 58

59 55

By analogy to the hydrocarbon anti-1,6:8,13-bismethano[14]annulene mentioned above, 55 turned out to be a highly reactive, purely olefinic molecule most likely to possess rapidly fluctuating double bonds. The loss of aromatic type π-electron delocalization in 55 is undoubtedly due to the severe puckering of the annulene ring that is evident from an X-ray structure investigation of the compound (37).

The synthesis of the potentially aromatic 54 proved to be quite a challenge since the exclusive anti-stereochemistry of the addition of difluorocarbene, as well as of all other carbenes tried, to the central double bonds of 56 frustrated the attempts to build up the compound by the established pathways. In order to get the CO-bridges into the syn-position eventually,




56 60 61 62 63 64 65 54

the rather sophisticated 1,6:8,13-propanediylidene[14]annulene 65 with three neighbouring hydroxyl groups at the $C_3$-bridge was envisaged as the strategic intermediate. Employing some relatively unusual methods, such as the conversion of an α-diazoketone into an α-bromo-α-diazoketone (38), 54 could be prepared via 60-65. Luckily, this effort paid off. Treatment of the triol 65 with periodic acid effected the anticipated expulsion of the central bridge carbon atom as formic acid with formation of the desired 54 as a stable aromatic compound.

The aromaticity of 54 manifests itself very convincingly in a comparison of its $^1$H NMR spectrum with that of its anti-isomer 55 (Fig. 2). While the spectra of the two compounds qualitatively conform in their patterns (singlet and AA'BB'-system), all of the resonances in the spectrum of 54 have experienced a downfield shift by ca. 1 ppm with regard to the corresponding resonances in the spectrum of 55. Taking also into account that the electronic spectrum of 54 grossly differs from that of 55, but closely matches that of syn-1,6:8,13-bismethano[14]annulene 52, it is obvious that a change from an olefinic to an aromatic 14π-electron system occurs as one goes from 55 to 54.

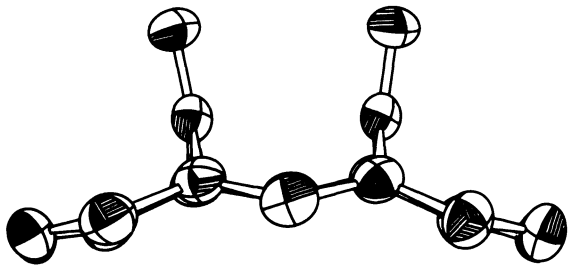


Fig. 1. X-ray structure of 15,16-dioxo-syn-1,6:8,13-bismethano-[14]annulene 54.

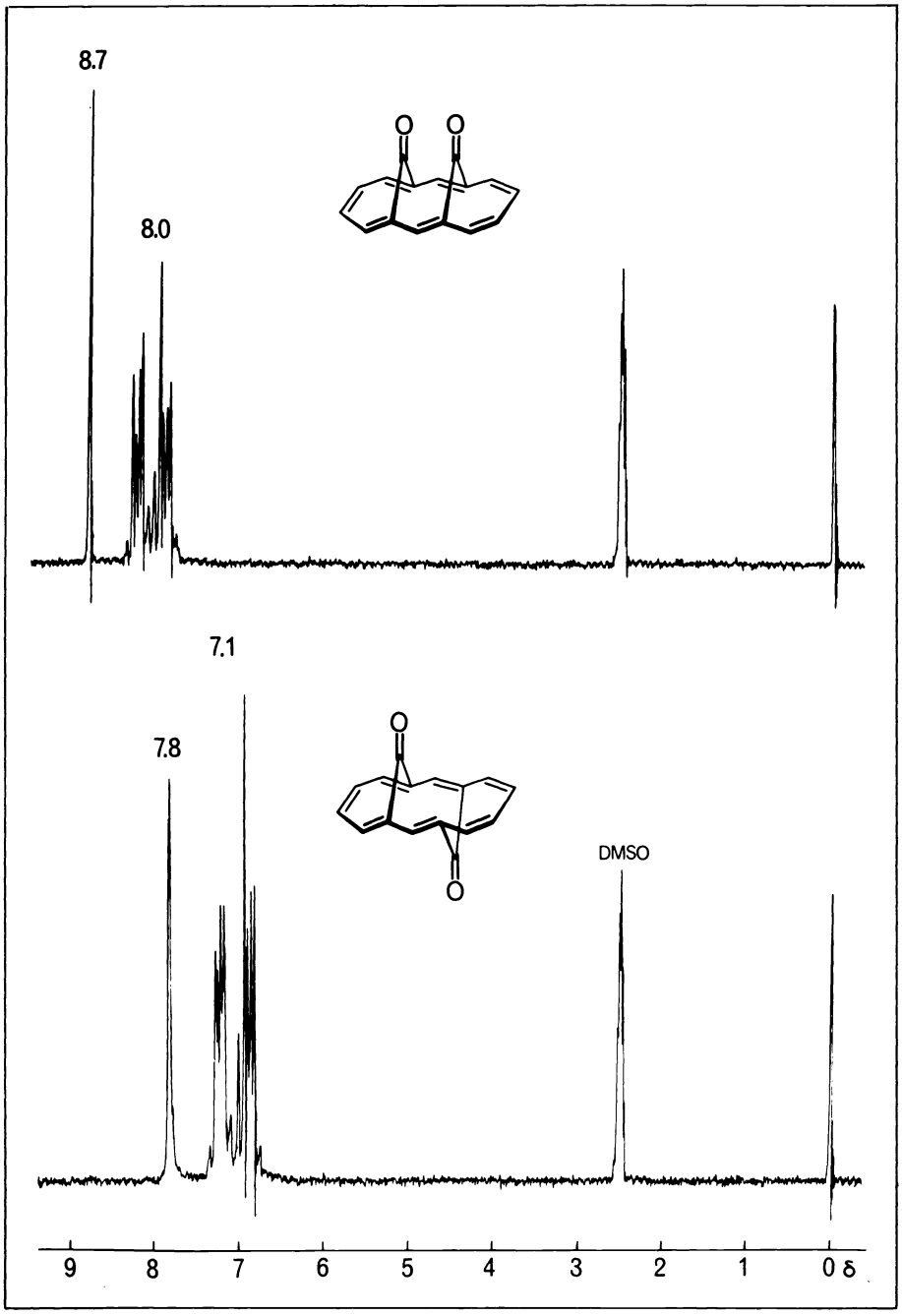


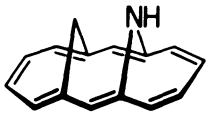

Fig. 2. $^{1}$H NMR spectra (90 MHz) of a) 15,16-dioxo-syn-1,6:8,13-bismethano-[14]annulene 54 and b) 15,16-dioxo-anti-1,6:8,13-bismethano[14]annulene 55 (in each case in DMSO-$d_6$, TMS as internal standard).

The similarity of the electronic spectra of 54 and 52 supports the conclusion drawn from a consideration of molecular models that the carbonyl groups and the annulene ring in 54 are effectively hindered from entering into conjugation with each other for steric reasons. Final proof of the aromaticity of 54 is provided by an X-ray structure analysis of the compound (Fig. 1) (39). Although the repelling steric and electrostatic interactions of the spatially close carbonyl groups in 54 impose some bending on the annulene ring, the carbon-carbon bond lengths in the ring, ranging from 1.376-1.413 Å, are typical of aromatic carbon-carbon bonds.

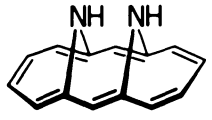
Chemically, the most remarkable property of 54 is its thermal stability. It seems hard to believe that this annulene - formally to be regarded as a "carbonyl complex" of anthracene - on being subjected to a vacuum flash pyrolysis at 500°C remains unchanged.

syn-1,6-Imino-8,13-methano[14]annulene 66

After having achieved the syntheses of 54 and 55 from 56, we felt that also syn-1,6-imino-8,13-methano[14]annulene 66 and syn-1,6:8,13-bisimino[14]annulene 67, which had been synthetic targets in this laboratory for quite some time, would ultimately become accessible through the hexahydroanthracene approach.




66




67

While these expectations have not yet materialized in the case of 67, compound 66 has now been obtained from 56 via 68-71 (40).

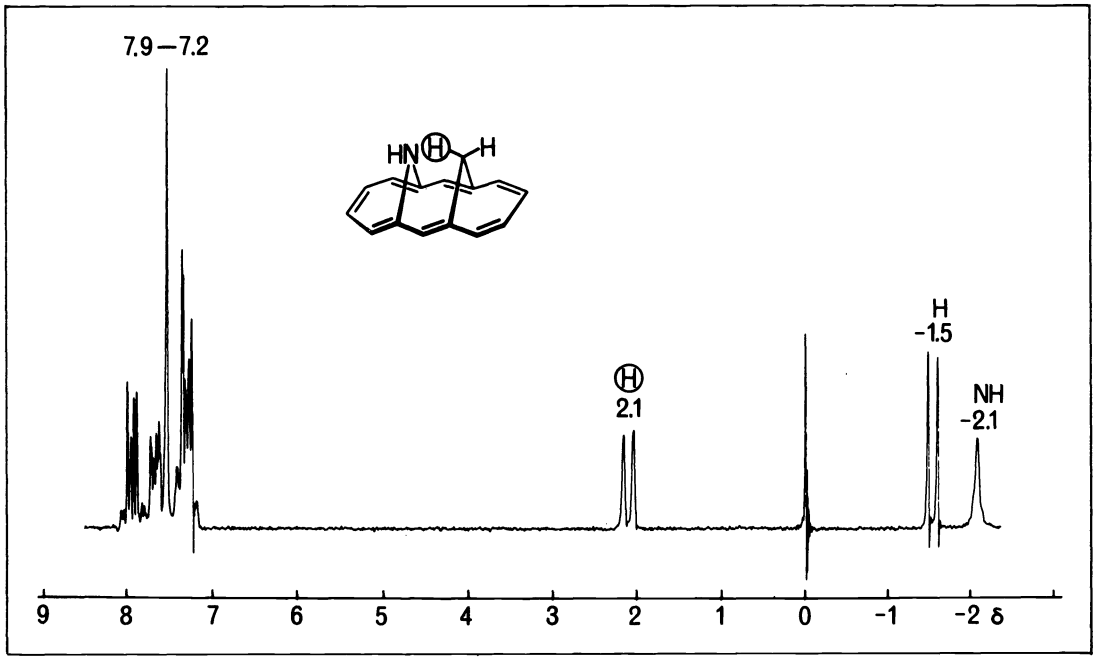
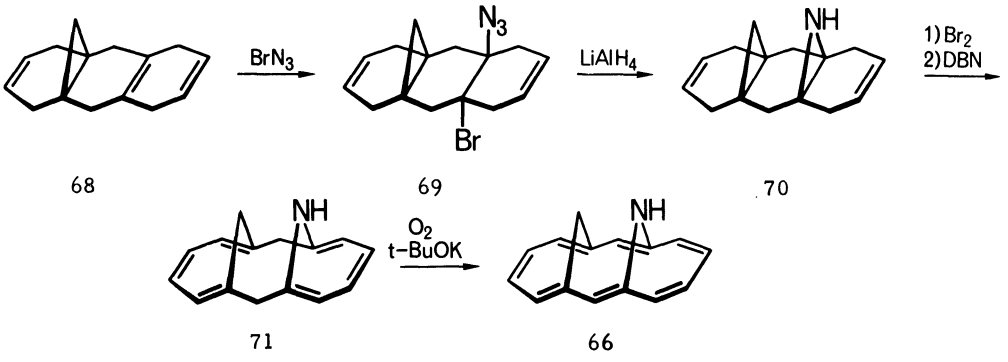



Fig. 3. $^{1}$H NMR spectrum (90 MHz) of syn-1,6-imino-8,13-methano-[14]annulene 66 (in $CCl_4$, TMS as internal standard).

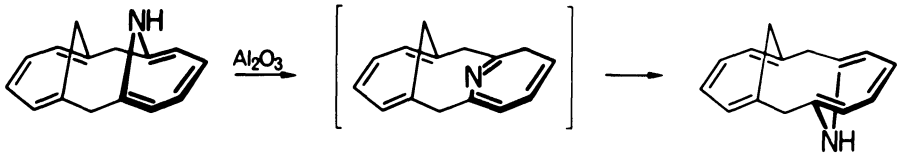
As evidenced by its $^{1}$H NMR spectrum (Fig. 3) and by structural data, 66 is an aromatic compound, as is 54. The chemical reactions of 66, specifically those associated with the bridge NH-function, are currently under investigation.



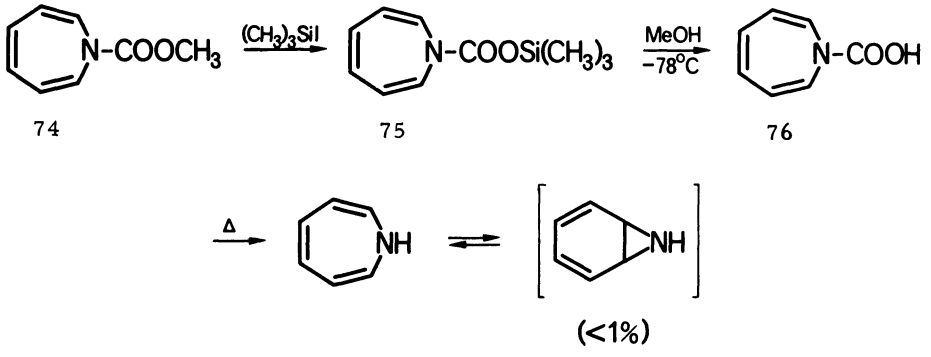

1H-Azepine and 3H-azepine 77 and 79

The synthesis of 66 has some interesting ramifications in azepine chemistry since it involves an intermediate, the dihydroannulene 71, which appears to be the first true 1H-azepine ever isolated and identified unequivocally.

In this connection it should be recalled that 1H-azepine 77 the parent of the well known N-substituted 1H-azepines developed by K. Hafner (41) has so far been encountered only as a transient. Previous efforts to prepare 77 by alkaline or acid hydrolysis of readily available 1-carboethoxy-1H-azepine had always led to complex mixtures of products, containing the tautomeric 3H-azepine 79 as a major component. This observation suggested that 77, once formed, is subject to a rapid prototropic shift rendering characterization of the compound very difficult.




Remarkably, the 1H-azepine 71 is rather stable thermally, surviving heating to 100°C in inert solvents unchanged (40). However, when 71 is chromatographed on basic alumina, it surprisingly rearranges by an inversion of one of the bridges to give its anti-isomer 73. We assume that this rearrangement is brought about by prototropic shifts in which the highly strained 3H-azepine 72 occurs as an intermediate. Evidently, the two stereoiso-



meric 1H-azepines 71 and 73 are favoured thermodynamically over their 3H-azepine tautomer 72 for steric reasons.

The properties of 71 suggested to us that there might be a chance to obtain the parent 1H-azepine 77 under strictly neutral conditions. Accordingly, 1-carbomethoxy-1H-azepine 74 was treated with trimethylsilyl iodide (42) and the trimethylsilyl ester 75 thus produced subjected to hydrolysis by methanol in the cold (-78°C). Contrary to expectation, the product of the latter reaction was not 77 but the carbamic acid 76, which actually could be isolated at low temperature. Heating 76 in chloroform briefly to room temperature and then cooling again afforded NMR spectroscopically pure 77 in solution (Fig. 4). Not too surprisingly in view of its previous record, the molecule is extremely unstable polymerizing fairly rapidly in chloroform and other solvents even at -30°C (43).

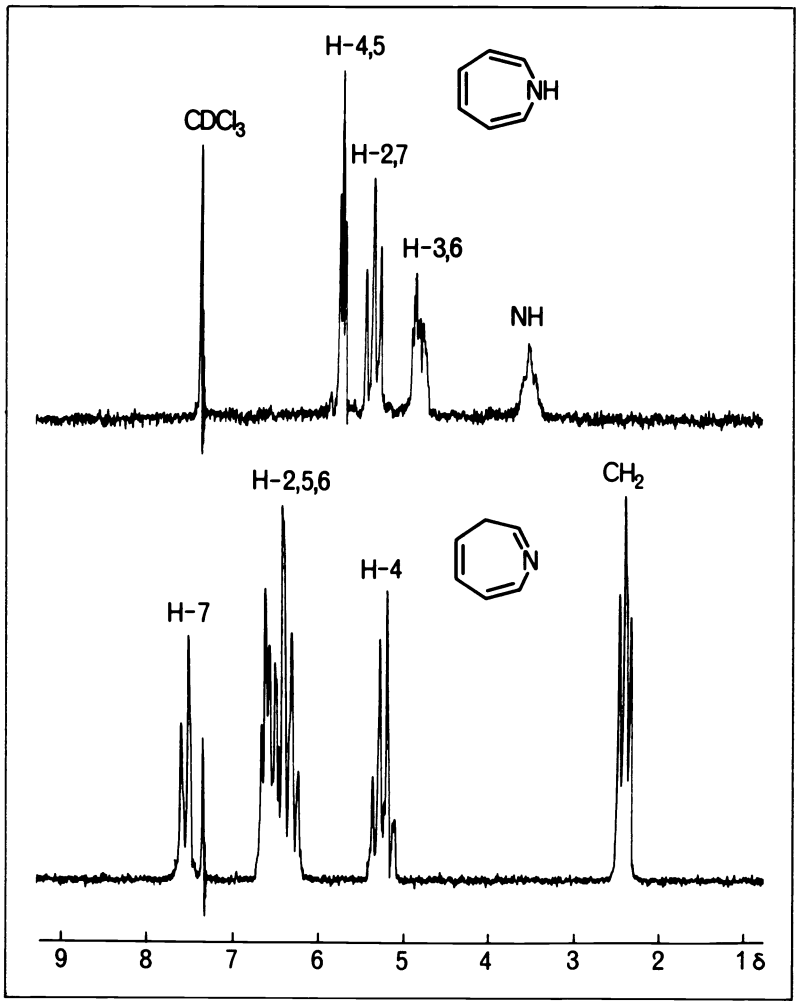
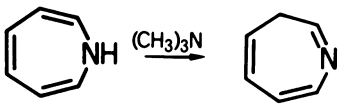



Fig. 4. $^{1}H$ NMR spectrum (90 MHz) of a) 1H-azepine 77 (-60°C) and b) 3H-azepine 79 (32°C) (in each case in $CDCl_3$, TMS as internal standard).

A detailed low temperature proton- and $^{13}C$ NMR investigation of 1H-azepine 77 finally allowed clarification of the much debated position of the hypothetical 1H-azepine – benzene imine equilibrium. Impressively confirming predictions based on MINDO-3 calculations by P.A. Kollman (44), we find 77 to exist virtually exclusively as the seven-membered ring tautomer, the concentration of the benzene imine tautomer 78 being below the detection limits of the methods applied, that is positively below 1 %.

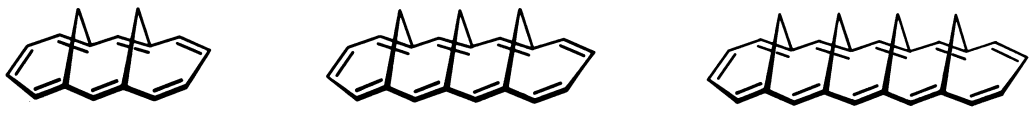
A chemical study of 77 confirms the great tendency of the molecule to tautomerize that was previously inferred by Hafner from the hydrolysis of 1-carboethoxy-1H-azepine. Catalytic amounts of acids or bases suffice to convert 77 into slightly more stable (distillable) 3H-azepine 79, the structure and uniformity of which is evident from its $^{1}H$ NMR spectrum.




77 79

## $CH_2$-BRIDGED [4n+2]ANNULENES BY A BUILDING-BLOCK APPROACH

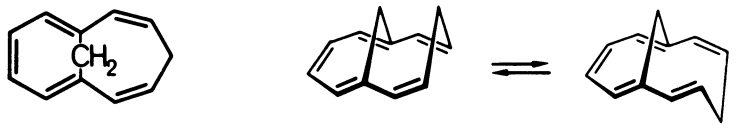
After this excursion into the azepine field I would like to return to my main theme and give you, in the last part of this lecture, a brief account of our recent successful efforts to synthesize – by a building-block approach – the 1,6-methano[10]annulene homologues (all-syn-series) syn-1,6:8,13-bismethano[14]annulene 52, syn,syn-1,6:8,17:10,15-trismethano-[18]annulene 80, and lately even syn,syn,syn-1,6:8,21:10,19:12,17-tetrakismethano[22]-annulene 81.



52 80 81

Molecular models indicate that 52, 80, and 81 must possess bent annulene rings due to the crowding of the juxta-positioned inner bridge hydrogen atoms. Nevertheless, these annulenes could be anticipated to qualify as aromatic molecules, as we had shown previously that the steric conditions for aromaticity are not very stringent.

syn-1,6:8,13-Bismethano[14]annulene 52 has been a synthetic goal for us from the outset of our studies on bridged annulenes, but all attempts to prepare the hydrocarbon from 56 had been futile. In order to overcome this impasse it obviously became necessary to devise an entirely new synthetic strategy. An approach to 52 deserving this description emerged from some unforeseen stereochemical findings on the known olefinic hydrocarbon bicyclo[5.4.1]-dodeca-2,5,7,9,11-pentaene 82 (45), a molecule which is closely related structurally to syn- and anti-1,6:8,13-bismethano[14]annulene.

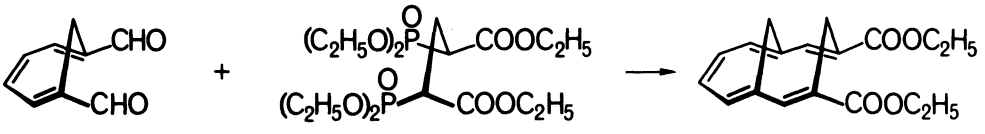



82 82a 82b

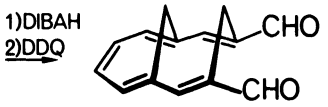
The hydrocarbon 82 should exist as an equilibrating mixture of the syn- and anti-conformers 82a and 82b, the two forms being interconvertible into each other by a flip of the peripheral $CH_2$-group. It seemed logical to assume that the anti-conformer 82b would be strongly favoured in the equilibrium, since it is devoid of the repulsive $CH_2$-hydrogen interaction believed to occur in the syn-conformer 82a. Surprisingly, however, spectroscopic evidence showed that one is dealing essentially with the syn-conformer 82a (46). The reason for the preferred existence of 82a appears to be better steric conditions for conjugation than are present in 82b. As revealed by molecular models, in the syn-conformer the terminal double bonds are favourably oriented for conjugation with the neighbouring double bonds of the cycloheptatriene moiety, whereas in the anti-conformer the terminal double bonds are almost at right angles to the adjacent double bonds.

83 83a

Assuming that the thermodynamic preference of the syn-conformer observed with bicyclo-[5.4.1]dodeca-2,5,7,9,11-pentaene 82, also extends to bicyclo[5.4.1]dodeca-2,5,7,9,11-pentaene-3,5-dicarboxaldehyde 83, this dialdehyde should make a most suitable synthon for the preparation of 52.

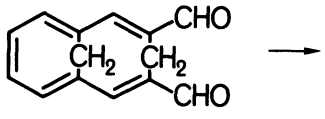


5 84 85



83

In this respect it was very important that we were able to develop an efficient three-step route (7) to 83 starting from readily accessible cycloheptatriene-1,6-dicarboxaldehyde 5. The crucial first step of this route is the Wittig-Horner reaction of 5 with the new bis-phosphonate 84, derived from α,α'-dibromoglutaric diethyldicarboxylate. Although literature reports on ring closure reactions utilizing bifunctional phosphoranes or phosphonates were not too encouraging, 85 is obtained in good yield. The subsequent conversion of 85 to 83 is then effected routinely by the reaction sequence of diisobutylaluminum hydride reduction and DDQ oxidation. According to spectral and structural evidence, the dialdehyde 83, indeed, exists as the syn-conformer 83a.



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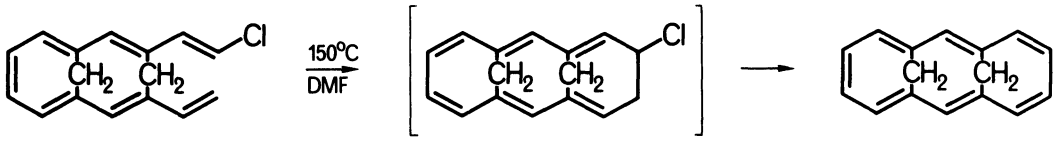


86 87 52

In search of an expedient pathway leading from 83 to 52 our attention focused on the annelation scheme that had proved to be useful in the synthesis of 1 (X=$CH_2$) from 5. In fact, all of the various versions of this scheme could be applied successfully to 83 (47). Best results were achieved when 86, readily prepared from 83 by successive treatment with methylene(triphenyl)phosphorane and chloromethylene(triphenyl)phosphorane, was chosen as the key intermediate. As anticipated, 86 on heating in dimethylformamide experienced a 14π-electrocyclic process and the cyclization product 87 thus formed spontaneously underwent elimination of hydrogen chloride furnishing 52 in good yield.

syn-1,6:8,13-Bismethano[14]annulene 52, a stable orange compound, fully shares the aromatic character of the bridged [14]annulenes 53 (n = 0,1,2,3) in physical respects but in contrast to the latter affords addition rather than substitution products on treatment with electrophilic reagents (1d).

The $^1$H NMR spectrum of 52 (Fig. 7) indicates that this [14]annulene bears an especially close relationship to 53 (n = 1) which is derived from 52 by replacement of its inner bridge hydrogen atoms by a $CH_2$-group. Thus, the resonances of the annulene protons, showing the familiar pattern of an AA'BB'-system and a singlet, occur in the range of $\delta$ = 7.1-7.9, whereas the resonances of the outer bridge protons appear as the X-part of the AX-system of the $CH_2$-protons at $\delta$ = -1.1. These values are virtually the same as those observed for the resonances of the corresponding protons of 53 (n = 1). As regards the resonances of the sterically interacting inner bridge protons constituting the A-part of the AX-system, these occur at $\delta$ = 1.0, i.e., more than 2 ppm downfield from those of the outer bridge protons. The location of these resonances at strikingly low field must be attributed to a large measure to a deshielding effect arising from the proximity of the inner bridge protons. In parallel with these NMR findings, the electronic spectra of 52 and 53 (n = 1) are in excellent agreement.

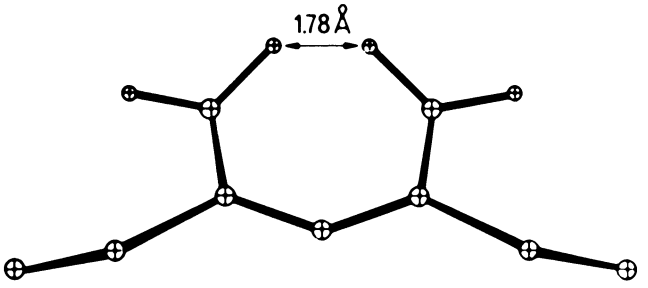
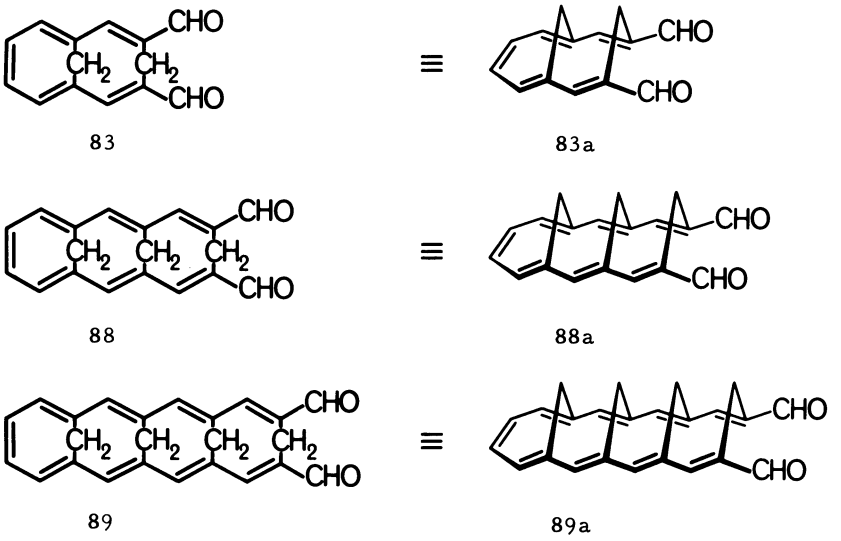



Fig. 5. X-ray structure of syn-1,6:8,13-bismethano[14]annulene 52.

The steric compression of the inner bridge hydrogen atoms of 52, as deduced from the molecular models and confirmed by the NMR spectrum, manifests itself most clearly in the X-ray structure determination of the hydrocarbon (Fig. 5) (48). The distance of these hydrogen atoms is found to be unusually short, measuring only 1.78 Å. To our knowledge, this is the shortest distance of non-bonded hydrogen atoms so far recorded for an organic molecule.




The existence of bicyclo[5.4.1]dodeca-5,7,9,11-pentaene-3,5-dicarboxaldehyde 83 as the syn-conformer 83a justified the assumption that its homologues 88 and 89 (all-syn-isomers) would likewise be present as the syn-conformers, i.e., 88a and 89a, respectively.

If this stereochemical premise would prove to be true, the synthesis of 88 and 89 should essentially be a matter of experimental effort and of the stability of the respective molecules. The obvious way to build up the α,ω-polyene dialdehydes 88 and 89 was to start from 83 and to apply to this compound, and subsequently to 88, the same homologation methodology, i.e., the three-step sequence of: 1) Wittig-Horner olefination by means of 84, 2) diisobutylaluminum hydride reduction, and 3) DDQ oxidation, that has served to convert 5 into 83. Attesting to the usefulness of this methodology, both homologations could be realized straightforwardly, affording a single stereoisomer in each case. Verifying the above stereochemical assumptions, X-ray structure determinations of these two next higher homologues of 83 showed them to be 88a and 89a, respectively. That the existence of 88 and 89 as the syn-conformers is not limited to the crystalline state, but, most importantly for the current project, also holds for the state in solution, is indicated by spectroscopic investigations.


90 80

The possession of the dialdehyde 88 in reasonable quantity promised ready completion of the synthesis of 80 by applying to 88 the annelation scheme that had led to 1(X=$CH_2$) and 52 from the respective dialdehyde precursors. In fact, successive treatment of 88 with methylene(triphenyl)phosphorane and chloromethylene(triphenyl)phosphorane afforded 90, and when this compound was subjected to thermolysis in boiling dimethylformamide, 80 was produced in good yield by the anticipated sequence of an 18π-electrocyclic process and an elimination of hydrogen chloride. Other versions of the annelation scheme have also been tried but were found to be less satisfactory (49).

syn,syn-1,6:8,17:10,15-Trismethano[18]annulene 80 is a bronze-coloured compound which, in striking contrast to its lower homologues 1(X=$CH_2$) and 52, shows a great tendency to polymerize. The olefinic reactivity of 80 seems to be caused, however, by Baeyer- and Pitzer-strain rather than by loss of resonance, for according to its spectroscopic properties the hydrocarbon exhibits distinct aromatic character.

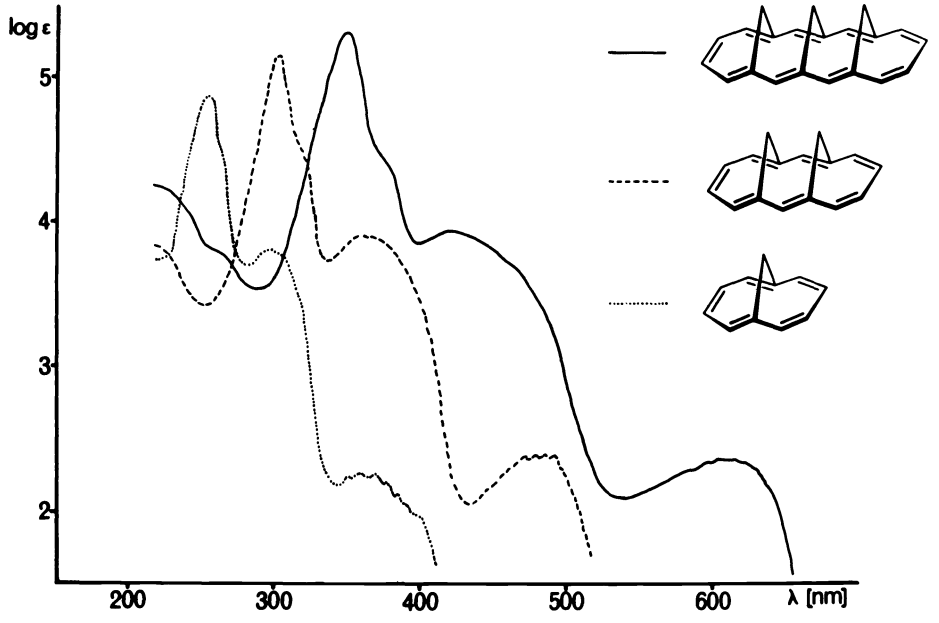



Fig. 6. Electronic spectra of 1(X=$CH_2$), 52, and 80 (in cyclohexane).

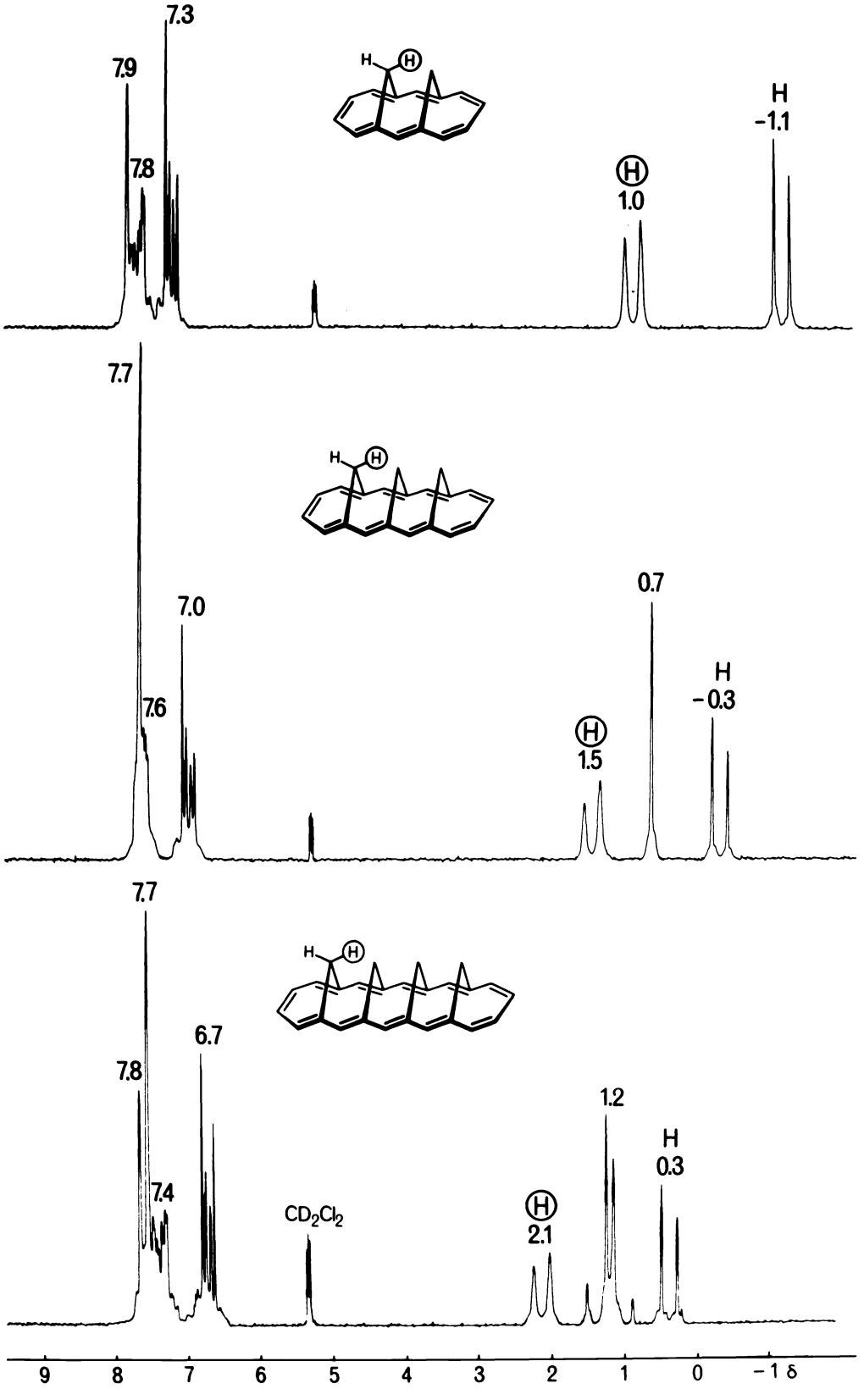
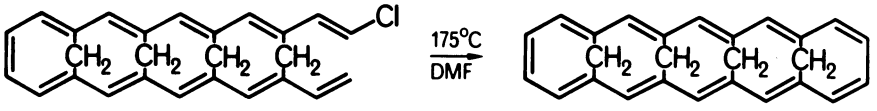



Fig. 7. $^1$H NMR spectra (60 MHz-FT) of a) syn-1,6:8,13-bismethano[14]annulene 52, b) syn,syn-1,6:8,17:10,15-trismethano[18]annulene 80, and c) syn,syn-syn-1,6:8,21:10,19:12,17-tetrakismethano[22]annulene 81 (in each case in $CS_2/CD_2Cl_2$, lock: $CD_2Cl_2$).

The most impressive evidence for the aromaticity of 80 is provided by the relationship of its electronic spectrum to those of 1 (X=$CH_2$) and 52. As seen from Fig. 6, the spectra of the three annulenes are remarkably similar in shape, but on going from [10]- to [14]- and [18]annulene all of the bands undergo bathochromic shifts, as theoretically predicted (50).

In parallel with these findings, the $^1$H NMR spectrum of 80 (Fig. 7) shows that the molecule sustains a diamagnetic ring current. Thus, the annulene protons give rise to an AA'BB'-system at $\delta$ = 7.3 and a singlet at $\delta$ = 7.7, and the bridge protons occur as an AX-system at $\delta$ = 1.5 and -0.3 (inner and outer protons, respectively, of the two outer bridges) and as a singlet at $\delta$ = 0.7 (protons of the central bridge). It is apparent, however, that the diamagnetic ring current in 80 has decreased as compared to that in 52. Due to its absorption pattern, the NMR spectrum also furnishes clear evidence that the expected syn, syn-stereoisomer having $C_{2v}$-symmetry is present, and not the syn, anti-isomer (likewise compatible with the configuration of the dialdehyde precursor). The nature of the crystals of 80 has so far not allowed an X-ray structure analysis of the compound.

The attempts to convert the dialdehyde 89 into 81 by the proven annelation scheme, i.e., via 91, met with difficulties which arose from the poor solubility properties and the instability of some of the compounds involved. It was only after a laborious study of the various reaction parameters that satisfactory conditions for the two successive Wittig olefinations and the subsequent cyclodehydrohalogenation could be found. Interestingly, the cyclodehydrohalogenation of 91, featuring a rate-determining 22$\pi$-electrocyclic process, requires slightly more rigorous conditions than are necessary for the corresponding reactions of 86 and 90.




91 81

syn, syn, syn-1, 6:8, 21:10, 19:12, 17-Tetrakismethano[22]annulene 81, thus finally brought to light, is a brownish-black compound that is even more prone to polymerize than 80 (51).

The $^1$H NMR spectrum of the compound exhibits the pattern expected for 81 with $C_{2v}$-symmetry (delocalized or rapidly fluctuating double bonds), since the annulene protons appear as an AA'BB'-system and two singlets (for two and four protons, respectively), whereas, correspondingly, the bridge protons occur as two AX-systems (Fig. 7). As inferred from the locations of the resonances of both types of protons (indicated in the spectrum) a diamagnetic ring current is present in the molecule, but has decreased further with respect to that in 52. The electronic spectrum of 81 could not yet be recorded accurately enough to justify its inclusion into Fig. 6. However, the data available already indicate that the spectrum is of the same type as those of its lower homologues (with further progression of all bands towards longer wave lengths). A more detailed discussion of the $\pi$-electron structure of 81 must await the outcome of the investigations currently in progress (52).

## CONCLUSION

The syntheses presented in the last section of this lecture constitute the experimental realization of a concept which we have pursued for a long time, namely the development of a homologous series of $CH_2$-bridged Hückel-type [4n+2]annulenes by a building-block approach.

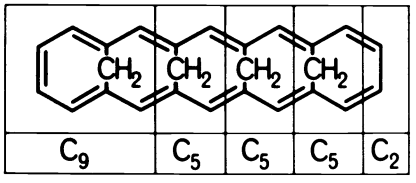
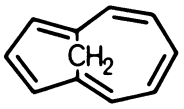



Fig. 8. Building-block approach to $CH_2$-bridged [4n+2]annulenes.

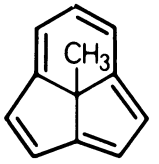
Let me recapitulate briefly the essentials of this approach by the schematic representation shown in Fig. 8. All of our syntheses start from the major building-block, the $C_9$-unit provided by the synthon cycloheptatriene-1,6-dicarboxaldehyde 5. Employing the homologation sequence, we attach one, two, or three $C_5$-units to the $C_9$-unit and thus arrive at the respective α,ω-polyene dialdehydes possessing syn-stereochemistry with regard to both configuration (refers to 88 and 89) and conformation. The desired $CH_2$-bridged annulenes with 14-, 18-, and 22π-electrons, respectively, are then obtained by adding the terminal $C_2$-unit by the three step sequence of Wittig-reaction, (4n+2)π-electrocyclic process and elimination. By leaving out the $C_5$-units this building-block approach also covers the synthesis of the parent 1,6-methano[10]annulene.

The synthetic scheme portrayed in Fig. 8 has the added virtue of being rather flexible in that, for example, the terminating step can be varied. This opens the prospect that also other series of $CH_2$-bridged (4n+2)π-electron systems, such as series of carbenium ions, carbanions, and azaannulenes will materialize. Provided that appropriate building-blocks will become available there is even a chance that series of bridged (4n+2)π-electron systems with bridges other than $CH_2$ can be developed.

Our investigations on bridged annulenes with a naphthalene or an acene perimeter constitute but one of the various avenues along which research on bridged annulenes is currently progressing. Much of the work carried out in this field in other laboratories harmoniously complements ours – and vice versa.




92

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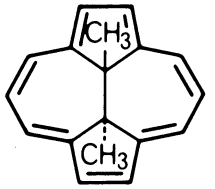
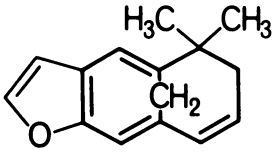



94

The existence and aromaticity of 1,6-methano[10]annulene 1 (X=$CH_2$) have inspired both S. Masamune (53) and L.T. Scott (54) to synthesize the isomeric 1,5-methano[10]annulene 92, a molecule closely related structurally to azulene. Although 92 has been predicted by molecular mechanics calculations to possess a rather distorted $C_{10}$-perimeter and hence to be olefinic, this [10]annulene also qualifies as an aromatic compound. Varying the geometry of the $C_{10}$-perimeter even further, C.W. Rees (55) has most recently been able to add the no less intriguing tricyclic hydrocarbon 7b-methyl-7bH-cyclopent[cd]indene 93 to the growing number of aromatic bridged [10]annulenes. In parallel with the situation in the bridged [10]annulene series, bridged [14]annulenes are known in three different versions. Apart from our bridged [14]annulenes with an anthracene perimeter there are V. Boekelheide's [14]annulenes (56) with a pyrene perimeter and it was again most recently that K. Müllen (57) reported the synthesis of trans-15,16-dimethyl-1,4:8,11-ethanediylidene[14]annulene 94, the first representative of bridged [14]annulenes with a dicyclopenta[ef,kl]heptalene perimeter.




95

In view of this diversity of bridged annulenes the question of whether nature might also be capable of generating this type of compounds does not seem to be too far-fetched. Actually, a natural product incorporating the 1,6-methano[10]annulene framework in its dihydro-stage has been uncovered lately by G. Cimino, S. De Stefano, L. Minale, and E. Trivellone (58). This Italian group has isolated from a Mediterranean sponge a furanosesquiterpene, called spiniferin-1, to which the dihydro-1,6-methano[10]annulene structure 95 – subsequently confirmed by J.A. Marshall (59) through synthetic studies – could be assigned.

The isolation of this compound indeed suggests that it might only be a matter of time until bridged [10]annulenes will be encountered as natural products!

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