SYNTHESES AND REACTIONS OF CYCLOBUTANE-FUSED SIX-MEMBERED HETEROAROMATICS

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Abstract — Syntheses of cyclobutane-fused heteroaromatics and their reactions via the corresponding heterocyclic diquinomethane intermediates are reviewed.

INTRODUCTION:

Since Cava and Napier[1] succeeded in preparing benzocyclobutene in 1956 thought to be an elusive molecule before that time,[2] this and its derivatives have been prepared by a variety of approaches. Jensen and Coleman[3] reported the formation of tetralin derivatives by thermolysis of 1,2-diphenylbenzocyclobutene in the presence of maleic anhydride and suggested the o-quinodimethane as an intermediate in 1958. In the middle of nineteen sixties, kinetic and stereochemical studies of this reaction confirmed the correctness of the Jensen's suggestion.[4,5] However, up to 1970, the main interest for benzocyclobutenes was directed primarily at determining how the fused benzene and cyclobutene rings interact with one another[6] and hence, concerned mainly on their physical properties.[7] In the early stage of nineteen seventies, Oppolzer published several papers stating that 1-substituted benzocyclobutene having an ene function at the terminus of the side-chain at the 1-position afforded upon thermolysis the annelated ring system in a regio- and stereoselective manner.[8,9,10] These results being contrasted with low regioselectivity of the intermolecular cycloadditions of benzocyclobutenes to olefins reported at that time,[11] stimulated the interest of synthetic organic chemists. Almost the same time as above, Kametani and his co-workers developed a new method for the total synthesis of isoquinoline and related alkaloids by thermolysis of benzocyclobutenes in the presence of imines or enamines and have attracted the interest of synthetic chemists participating in alkaloid and heterocyclic fields.[12,13,14]

At present, intramolecular (or in some cases, intermolecular) cycloaddition reactions of o-quinodimethane (formed in situ by thermolysis of benzocyclobutenes or by other methods) for regio- and stereoselective synthesis of polycyclic ring system have become one of the fundamental synthetic methods. The wide scope as well as utility of this type of reactions in organic syntheses have been explored mainly by two independent research groups headed by Oppolzer and Kametani, and some of these works have appeared as reviews.[15,16]

Though 1,2-dihydrocyclobuta[b]quinoline,[17,18] 1,2-dihydrocyclobuta[b]- and -[c]-pyridines,[19,20] were synthesized by the middle of nineteen seventies, there is no paper concerning with their use to such cycloadditions before 1980, and only their physical properties have been studied in some detail. The reason for the lack of studies on their chemical reactivity may at least partly be due to the lack of efficient synthetic method for them. In 1979, we discovered a simple synthetic method of 1,2-dihydrocyclobuta[c]quinolin-3(4H)-one derivatives by two steps from readily available 4-alkoxy-2-quinolone.[21] By this two-step procedure, the former compounds can be obtained from the latter in 80-90% overall yields. In the next year, we found for the first time using these cyclobutaquinolones that cyclobutane-fused heteroaromatics could also react with olefin in both intra- and intermolecular manner.[22]

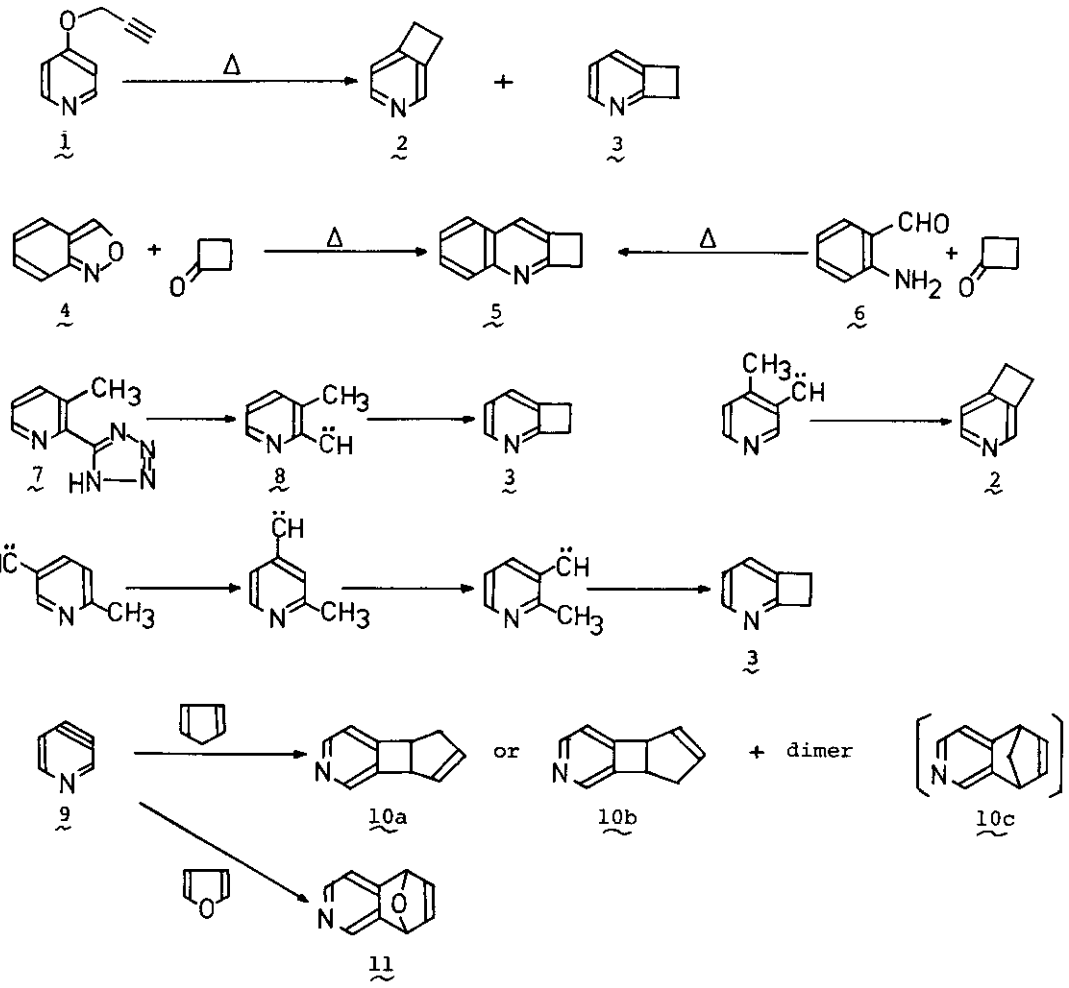
This review delinates the scope and limitations of inter- and intramolecular cycloaddition reactions of aza- and oxa-heterocyclic analogues of the o-quinodimethanes with olefin. A summary of the available routes to cyclobutane-fused heteroaromatics is given first, followed by specific examples which illustrate the use of hetero-analogues of benzo- and naphthocyclobutenes as useful synthons for polycyclic ring system containing at least one heteroaromatic ring.

I. SYNTHETIC METHODS OF CYCLOBUTANE-FUSED SIX-MEMBERED HETEROAROMATICS:

I. 1. SOME EARLIER SYNTHETIC METHODS:

Up to 1979, there is no systematic method for the synthesis of the title compounds. Trahanovsky and his co-workers have reported that pyrolysis of propargyl 4-pyridyl ether (1) at 550° produces both isomers (2 and 3) of 1,2-dihydrocyclobutapyridine.[19a] Necessary separation of the two isomers having quite similar properties each other and use of flash vacuum pyrolysis technique seem to indicate the method to be unsatisfactory for preparative purpose. The synthesis of 1,2-dihydrocyclobuta[b]quinoline (5), the first heterocyclic analogue of naphthocyclo-

butene, was reported by Wilk et al., who obtained 5 in a low yield from a sealed tube reaction of anthranil (4) with cyclobutanone in the presence of mercuric sulphate.[17] A little later, Markgraf and Scott synthesized 5 via a Friedländer synthesis of o-aminobenzaldehyde (6) with cyclobutanone in 55% yield.[18] Another entry to aza analogues of benzocyclobutenes is the intramolecular trapping of picolylcarbenes (e.g., 8) formed by thermolysis of the corresponding picolyltetrazoles (7). When the two groups (CH_3 and :CH) are not originally ortho related, the reaction proceeds by carbene-carbene rearrangement.[20] Though this method may be applicable for the synthesis of substituted derivatives,[23] it suffers from relatively low yields. 1,2,4,5-Tetrahydrodicyclobuta[b,e]pyridine has been prepared by such a method.[24] Though cyclopentadiene reacted with 3,4-pyridyne (9) to give the adduct[25] (10a or 10b) together with the 3,4-pyridyne dimer, the structure determination is not enough to exclude the other possible structure (10c).[26]



I. 2. KANEKO-NAITO METHOD: TWO-STEP PROCEDURE FOR THE PREPARATION OF THE TITLE COMPOUNDS:

Since 1979, we have developed a novel photochemical method for the synthesis of cyclobutane-fused heteroaromatics starting from heteroaromatics involving β-alkoxy (or its equivalent group) enone function in their ring system. General scheme of this method is summarized in Chart 1. The enone function involved in a heteroaromatic ring (A) is added photochemically to a variety of olefins to give the 2+2 adduct (B). This addition reaction proceeds in most cases in a regio-selective manner and the head-to-tail adducts are formed exclusively or at least as major product, irrespective to the olefin used. Treatment of the adduct with base (or acid) then affords the heteroaromatics annelated with a cyclobutane ring on the ene function of the starting enone system (C). In the second step, the alkoxy group acts as a leaving group and the driving force of this step is provided at least partly by the gain of heteroaromatic system.

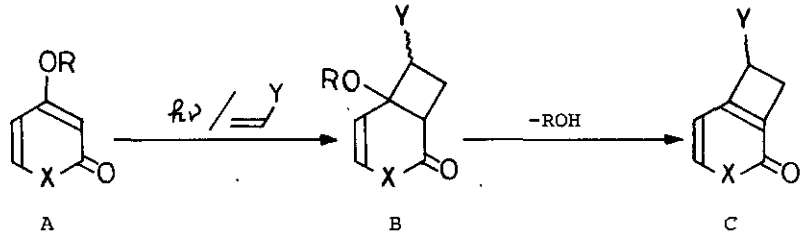
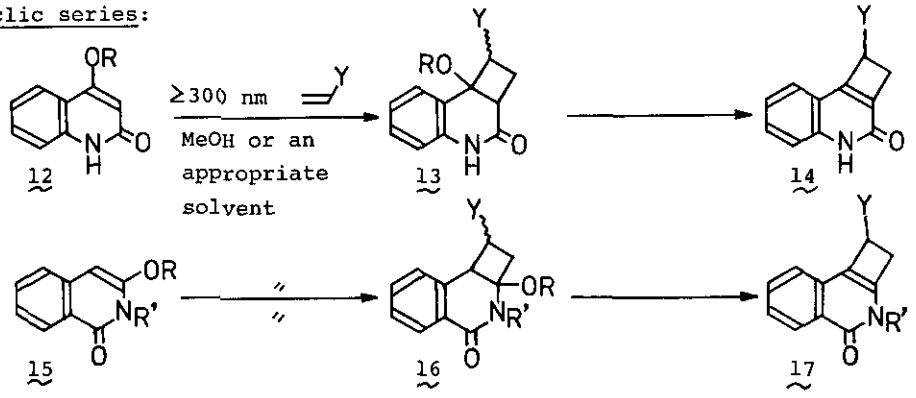
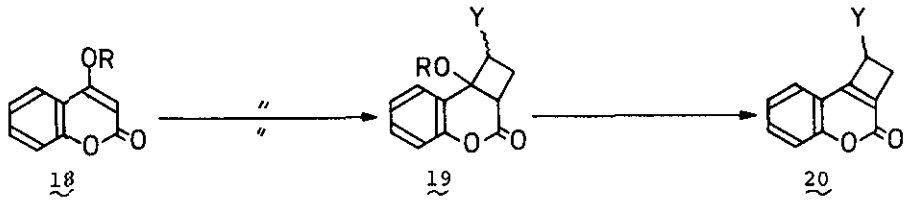


Chart 1 (X=heteroatom)

This two-step procedure was first found by Kaneko and Naito for 4-alkoxy-2-quinolone[21] (12) and successfully extended to 3-alkoxy-1-isoquinolone[27] (15), 4-alkoxy derivatives (21, 18, and 26) of 2-pyridone,[28] coumarin,[29] pyrone,[30] and to 6-chloro-1,3-dimethyluracil[31] (29) (Chart 2).

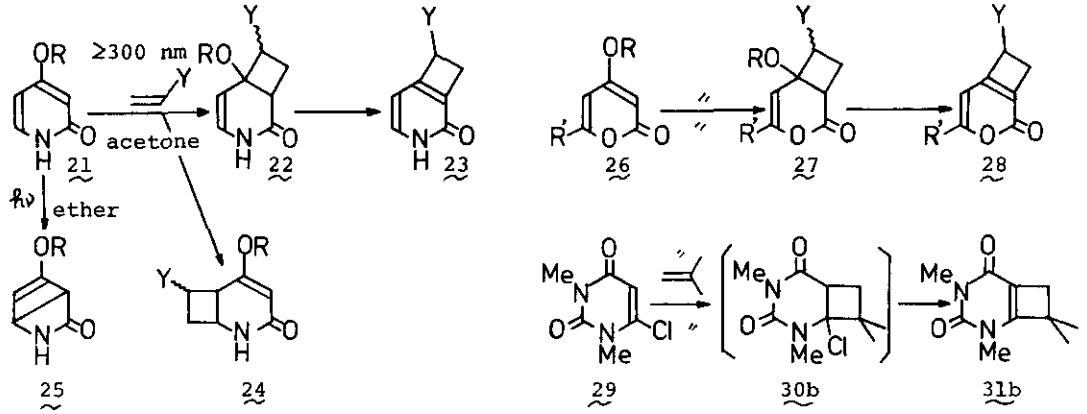
bicyclic series:





18 19 20

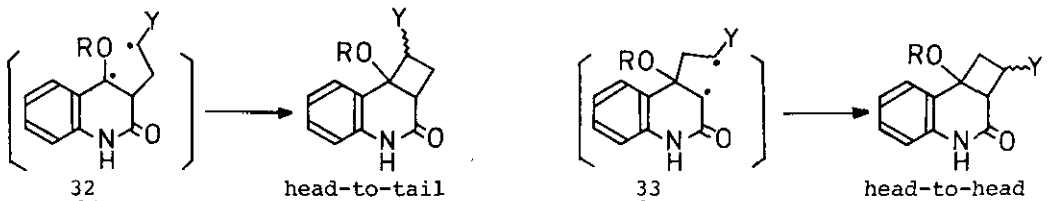
monocyclic series:



21 22 23 25 24 26 27 28 29 30b 31b

Chart 2

In bicyclic heteroaromatics, the photoaddition to olefins proceeds at ≥300 nm in methanol (or any other transparent solvent). In monocyclic series, however, acetone must be used as sensitizer. This fact as well as the addition product obtained as major one has always head-to-tail structure pointed that the addition reaction proceeded via the triplet excited state of these heteroaromatics (vide infra). Necessity of the sensitizer in monocyclic series simply reflects that the intersystem crossing from S_1 to T_1 is far less efficient in these compounds than that in the bicyclic series. Furthermore, a regioselective formation of the head-to-tail adduct indicates that the reaction proceeds in a stepwise manner via the biradical intermediates (32). Obviously, the biradical (32) should be more



32 head-to-tail adduct (13) 33 head-to-head adduct (13')

stable than the other biradical (33). The stepwise mechanism is also supported by the lack of stereoselectivity (in most cases) in these photoaddition reactions.

In aza-heteroaromatic series, the base treatment (NaOMe/MeOH or NaOH/MeOH, room temp.~reflux) is enough to effect the elimination of ROH from the adducts to give the final products. However, the use of a Lewis acid such as BF_3-Et_2O in an aprotic solvent (room temp.~reflux) is necessary for this step in coumarin and pyrone series. This is because either acid or base in a protic solvent causes the solvolysis of the lactone ring in the adduct to give the ring opened product[29] (Chart 3).

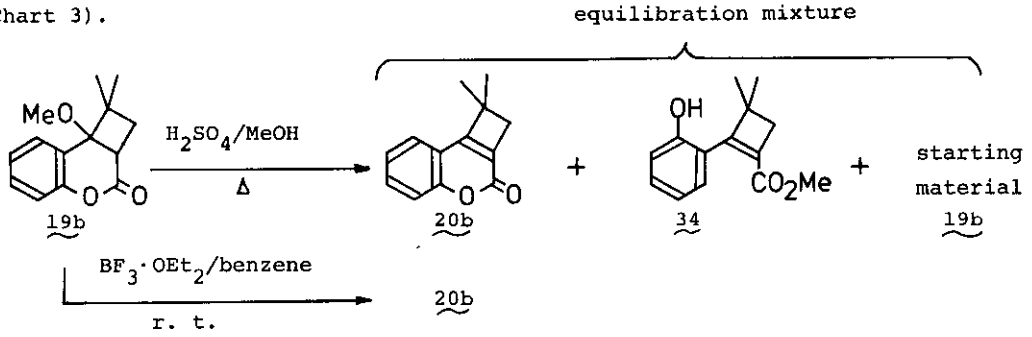


Chart 3

Reid and co-workers[32] who originally accomplished the transformation shown in Chart 4 for coumarin series, found that pyrolysis of the acetate (19c) gave the cyclobutene (20c) and products (37 and 38) derived therefrom. However, pyrolytic elimination of an acetic acid is obviously not suitable for the selective formation of 20c (see the following section).

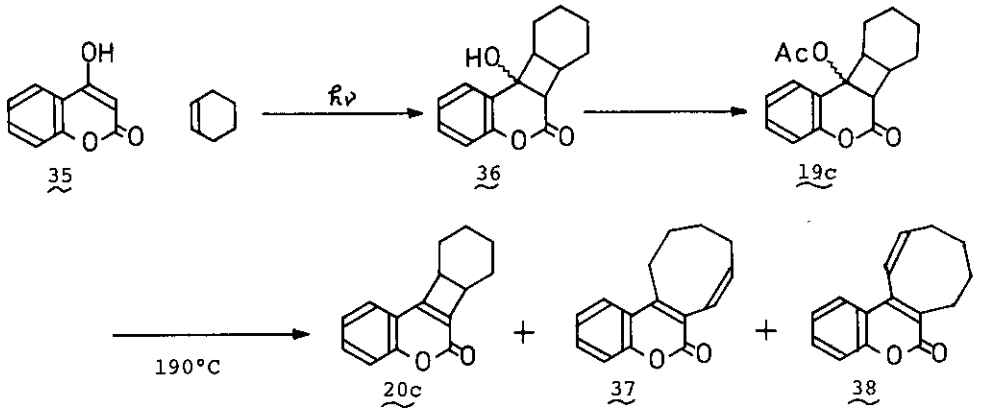
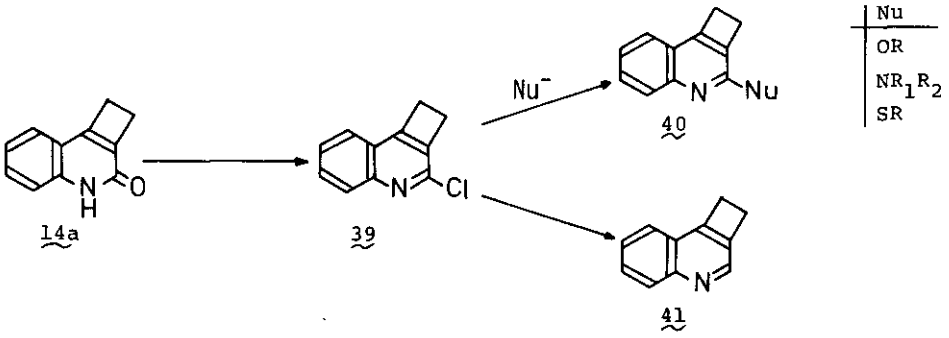


Chart 4

In case where an acid or base is used, the elimination of ROH from the adducts occurs irrespective to their stereochemistries.[33] Hence, so far as the adducts

have the head-to-tail structure (B), one kind (C) of cyclobutane-fused heteroaromatic compounds is formed by the above two-step procedure in high overall yields (80-90%).

The 1,2-dihydrocyclobuta[c]pyridones and -quinolones thus formed are easily transformed to the corresponding 3-chlorides (e.g., 39), whose chlorine atom is replaced by a variety of nucleophiles to give the corresponding 3-substituted cyclobutapyridines and -quinolines.[34] These 3-chloro derivatives also serve as the starting materials for 1,2-dihydrocyclobuta[c]pyridine and -quinoline (2 and 41). Thus, reductive dechlorination of these chlorides by zinc in acetic acid afforded the corresponding bases in high yields.[34,35]



14a 39 40 41

4-Acetoxy derivatives can also be used as starting materials for the above two-step procedure. Thus, for example, 4-hydroxy-2-pyridone or -quinolone can be acetylated selectively to the corresponding 4-acetoxy derivatives under usual conditions. The adducts obtained from 4-acetoxy-2-pyridones and -quinolones are, in most cases, stable enough to isolate, but some of them lose acetic acid even upon attempted purification of the adduct by silica gel column chromatography.[36] More facile elimination of the 4-substituent from the adduct was observed when 4-tosyloxy-2-quinolone was reacted photochemically with alkenes in acetone. T.l.c and UV spectral measurement of the irradiated solution indicated the direct formation of the corresponding cyclobutenes.[37] Some examples are shown in Chart 5.

It should be noted that, while bicyclic series poses no problem in the photocycloaddition to olefin and give exclusively the desired type of adduct irrespective to the olefin used, monocyclic series has two problems: 1) Without sensitizer, the photopyridone (e.g., 25) or photopyrone is formed via the S_1 state. Thus, for example, 4-methoxy-2-pyridone (21a) upon irradiation in ether gave the corresponding photopyridone [25a: 25 (R=Me)] irrespective to the presence or ab-

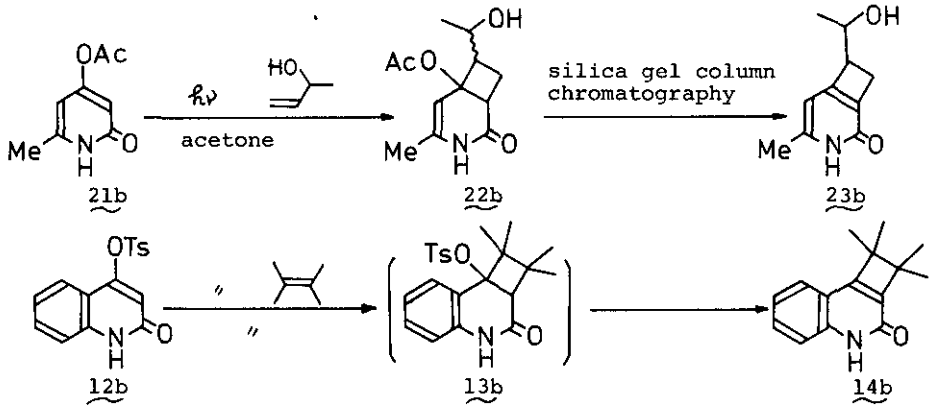
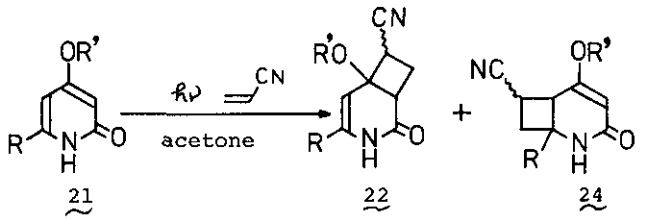


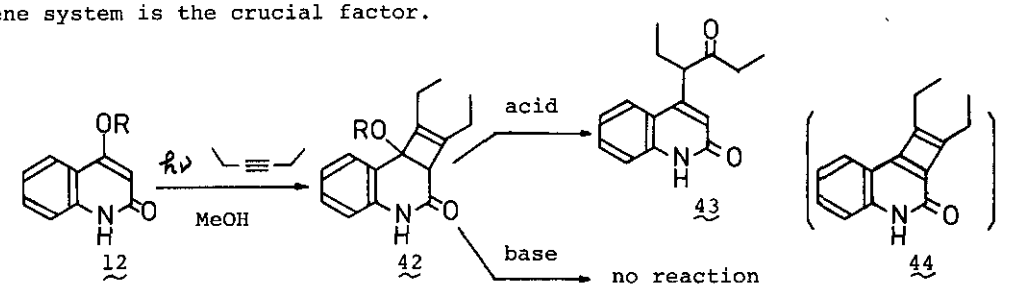
Chart 5

sence of olefin.[38] 2) For 4-alkoxy- or 4-acetoxy-2-pyridone, the addition to electron-rich olefins is far faster than that to electron-deficient olefins. Furthermore, in the addition to electron-deficient olefins, the other type of adduct (24) are formed as the major product, and the desired adduct (22) becomes the minor one.[28,36] The adduct (22) becomes again the major product, if the starting pyridone carries an alkyl group (e.g., 21b) at its 6-position.[36]

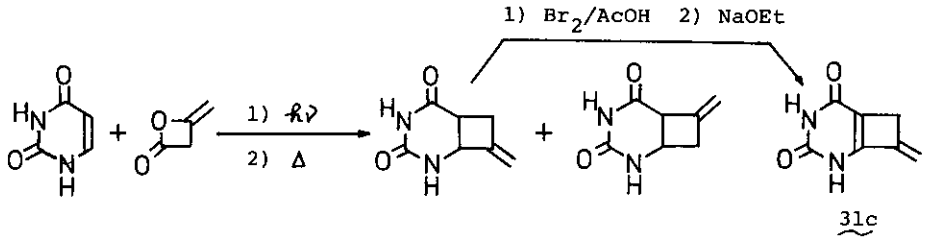


	relative amonut	
R	22	24
H	1	2
Me	5	1

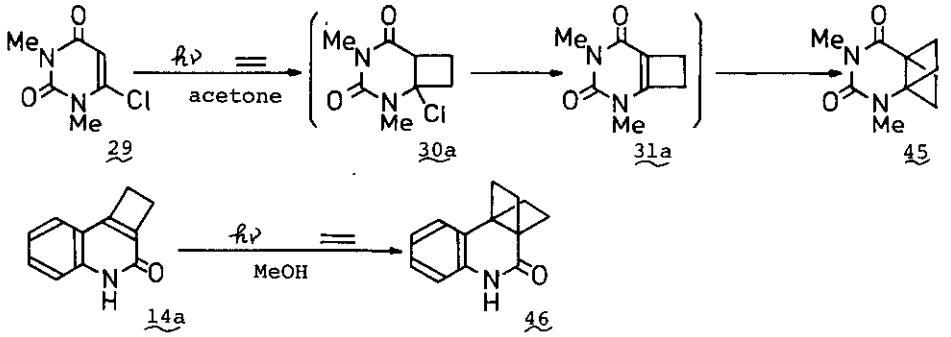
The elimination of ROH from the adduct obtained from 4-alkoxy- or -acetoxy-2-quinolone with olefin occurs smoothly without exception. However, the adduct formed from these quinolones and alkyne did not give the corresponding cyclobutadienes (e.g., 44) under these conditions.[39] Probably, antiaromaticity of a cyclobutadiene system is the crucial factor.



Photodimerization typical to 2-pyridones, 2-quinolones, coumarins, etc. did not occur for these 4-alkoxy derivatives. Though 4-acetoxy-2-quinolone (12: R=Ac) dimerized slowly upon irradiation, this can be prevented by performing the irradiation in the presence of a large excess of olefin.[39] As shown in Chart 2, photoaddition of the 6-chlorouracil (29) to isobutene proceeds regioselectively to give 31b (via unstable 30b). Hence, the presence of chlorine atom at the 6-position of uracil ring endorses regioselectivity to the photoaddition.[40] Very recently, Kato et al. synthesized 31c through multi-step starting from uracil and diketene.[41]



Our two-step procedure, if applied to 6-chloro-1,3-dimethyluracil (29) using ethylene as an olefin led after irradiation step to direct formation of the propellane (45).[31] In this connection, it seems to be noteworthy that 1,2-dihydrocyclobuta[c]quinolin-3(4H)-one (14a) also afforded the corresponding propellane (46).[39] Such propellane formation is only dominant when ethylene is used as an olefin.



The photochemical intermolecular 2+2 addition reactions have also been applied to the intramolecular ones. Thus, for example, irradiation of 4-allyloxy-2-quinolone (12c) in methanol resulted in regio- and stereoselective formation of the tetracyclic compound (47), which eliminated methanol by base to give 2-hydroxymethyl compound (48). None of the corresponding 1-hydroxymethyl compound (14: R= CH_2OH, the compound synthesized by our two-step procedure from 12 and allyl-alcohol) was obtained. In this case, the reaction probably proceeds under kinetic

control. The cross addition product is still obtained from 4-(but-3-enyloxy)-2-quinolone, but only the parallel addition product is formed from the quinolones having longer methylene chain.[42] Quite recently, Kato and co-workers synthesized 2,4-dimethyl-1,2-dihydrocyclobuta[c]quinolin-3(4H)-one (49) by the route as shown in Chart 6.[43]

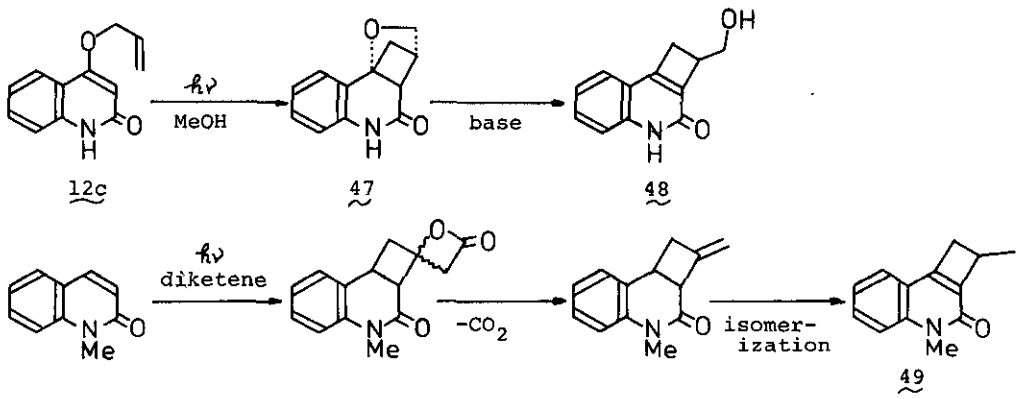
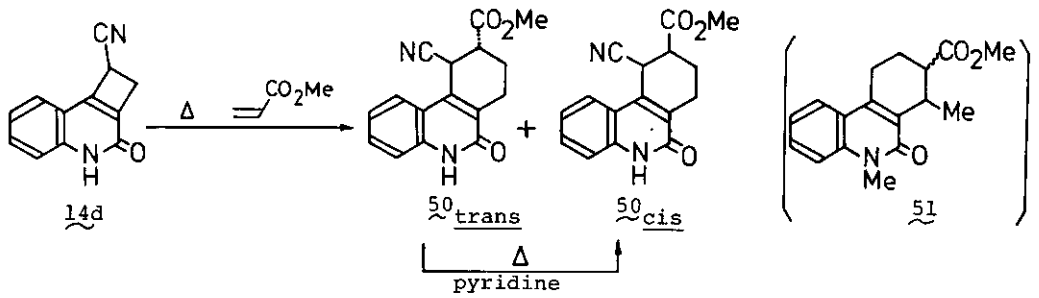


Chart 6

II. INTERMOLECULAR CYCLOADDITION REACTIONS OF SIX-MEMBERED HETEROCYCLIC o-DIQUINOMETHANE (GENERATED in situ FROM CORRESPONDING CYCLOBUTANE-FUSED HETEROAROMATICS)

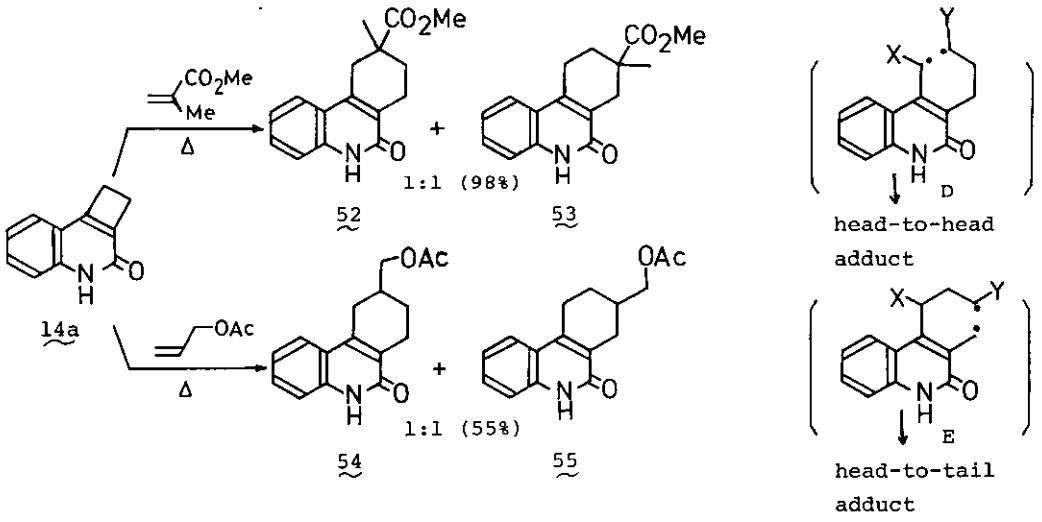
The 4+2 cycloaddition of 2-quinolone-3,4-diquinomethane species generated in situ from 1,2-dihydrocyclobuta[c]quinolin-3(4H)-ones to olefin was reported by us in 1980[22] and this experiment provided the first example of the application of the benzocyclobutene method[15,16] to heteroaromatic series. Thus, heating the 1-cyano derivative (14d) in xylene at 100°C in the presence of 30 mol. equiv. of methyl acrylate resulted in the formation of a crystalline adduct in 90% yield. PMR spectrum showed it to be a mixture of two stereoisomers both having a head-to-head structure (50_{trans} and 50_{cis} in ca. 2:1 ratio). Heating of 50_{trans} in pyridine-d_5 at 100°C for 15 hr afforded the inseparable mixture in which 50_{cis} predominated over 50_{trans} (50_{trans} and 50_{cis} in ca. 3:4 ratio). This clearly indicates that cycloaddition reaction proceeds under kinetic control, being the major isomer (50_{trans}) less stable thermodynamically than the minor one (50_{cis}).

Other electron-deficient olefins also reacted with 14d under the same condition to give mixture of two stereoisomers, in which the major one was always thermodynamically less stable than the minor one. In all products obtained by using 1-cyano derivative as masked o-diquinomethane, the head-to-head structure is assured.



The 4+2 cycloaddition of the parent cyclobutaquinolone (14a) to olefin, however, showed no regioselectivity and two regioisomers were obtained in nearly equal amounts.[39] For 14a, allyl acetate (an electron-rich olefin) also gave the corresponding cycloadduct, though much longer reaction time compared to an electron-deficient olefin was necessary and the yield of the adduct was decreased. Kato et al. reacted 49 with methyl acrylate and obtained a single isomer (51) as the product.[43]

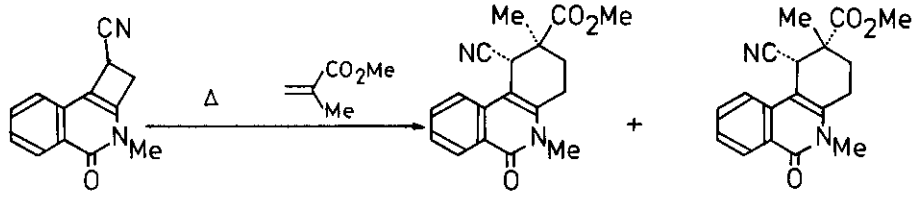
These facts suggest that the relative stability of the biradical intermediates (D and E) is almost the same for the parent series (X=H in formulae D and E) and the 1-cyano substituent stabilizes D (X=CN) preferencially, while 2-methyl group stabilizes E.



Contrary to the ease of cycloaddition reactions between 14d and electron-deficient olefins, electron-rich olefins (e.g., allyl acetate, cis 2-butene-1,4-diol, etc.) did not react with 14d under these conditions, and only dimer[44] of 14d was obtained after a prolonged reaction period.

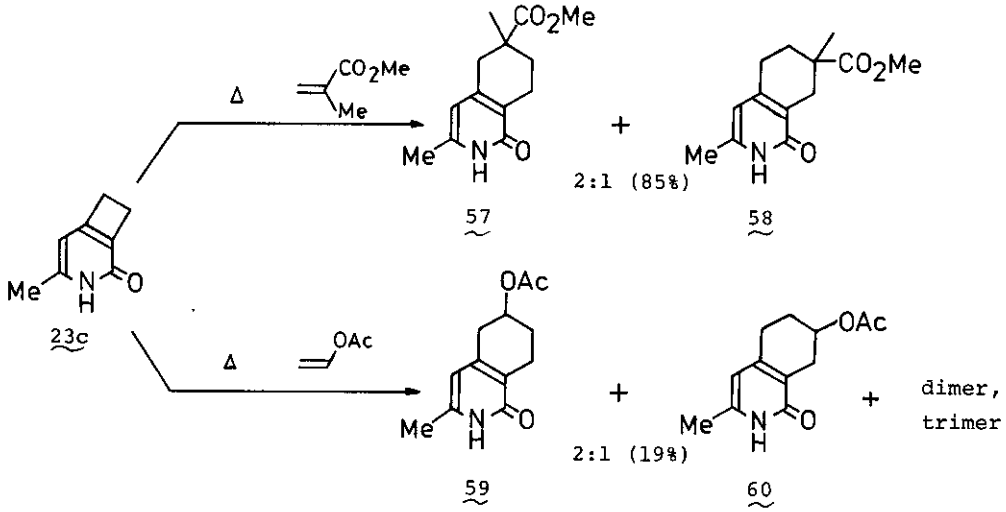
The above results showed that 1,2-dihydrocyclobuta[c]quinolin-3-ones (14) reacted with olefins in the same manner as benzocyclobutenes. Also, high regioselectivity is expected for the cycloaddition reaction, if the cyclobutene ring carries a substituent either on its 1- or 2-position.

1,2-Dihydrocyclobuta[c]isoquinolin-4(3H)-ones having a substituent at the 1-position also reacted with olefins to give the 4+2 adducts. The reaction again proceeds in a regioselective manner.[27]

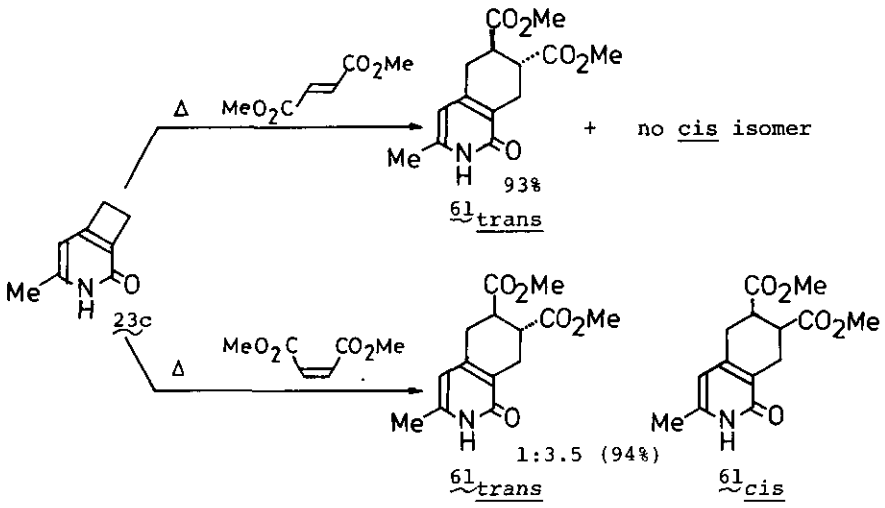


17c 56 trans 56 cis

The same situation as in the case of aza-naphthocyclobutenes was found to exist in the cycloaddition of the cyclobutapyridones (23) to olefins. Thus, the addition proceeds without any regioselectivity if no substituent is present on the cyclobutene ring.[45,46] Thus, for example, 5-methyl-1,2-dihydrocyclobuta[c]pyridin-3(4H)-one (23c) upon heating in o-dichlorobenzene in the presence of methyl methacrylate or vinyl acetate gave in each case two possible regioisomers. However, 6-substituted tetrahydroisoquinolones predominate over 7-isomers.

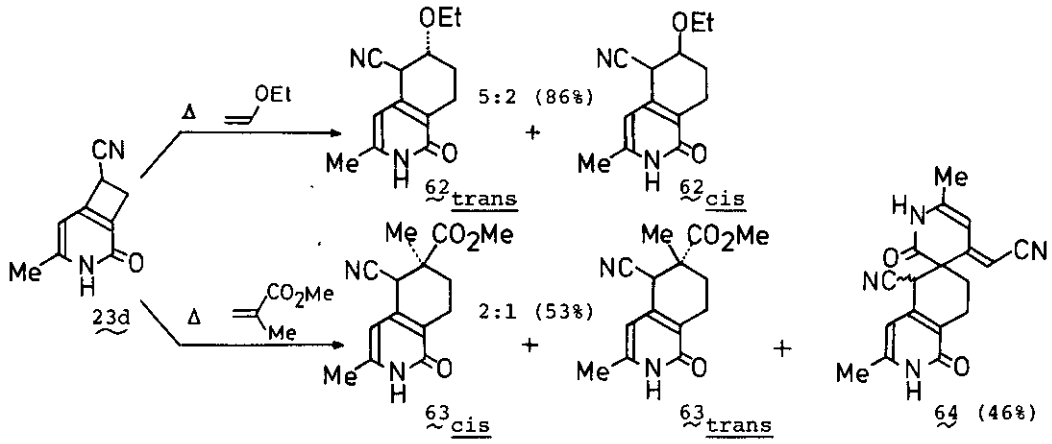


The reaction also proceeds non-stereoselectively. Thus, while dimethyl fumarate gave exclusively the trans diester, dimethyl maleate afforded both of trans and cis isomers in ca. 1:3.5 ratio. This fact again supports the participation (at least partly) of the biradical intermediate (e.g., D).



In order to examine the effects of substituent in more detail, Kaneko and Momose[30,45] reacted 1-cyano- and 1-ethoxy derivatives (23d and 23e) with a variety of olefins. The results are summarized as in the following. 1) The presence of substituent at the 1-position endorses the reaction proceed regioselectively and hence, 5,6-disubstituted tetrahydroisoquinolones are formed exclusively by the reactions with mono-substituted olefins. 2) 1-Cyano derivative (23d) reacted with an electron-rich olefin much faster than with an electron-deficient one. Thus, if the corresponding diquinomethane is actually the intermediate, the cycloaddition of the 1-cyano derivative to olefins belongs to Diels-Alder reaction with inverse electron demand.[47] Thus, an appreciable dimer formation was observed when 23d was reacted with methyl methacrylate. On the contrary, the 1-ethoxy derivative (23e) reacted only with an electron-deficient olefins, and hence, the reactions of 23e with olefins belong to normal Diels-Alder reaction. The dimer (65) was the sole product, if 23e was heated in o-dichlorobenzene alone or in the presence of an electron-rich olefin. These results are summarized in Chart 7.

Taking these findings into consideration, the intermolecular 4+2 cycloaddition reactions of 23 with olefins seem to be applicable for the synthesis of some alkaloids (e.g., yohimbine, reserpic acid, olivacine, ellipticine, etc.).


OEt
NC
CN
Δ
OEt
5:2 (86%)
+
Me
N
H
O
62 trans
62 cis
23d
CO2Me
Me
2:1 (53%)
63 cis
63 trans
64 (46%)

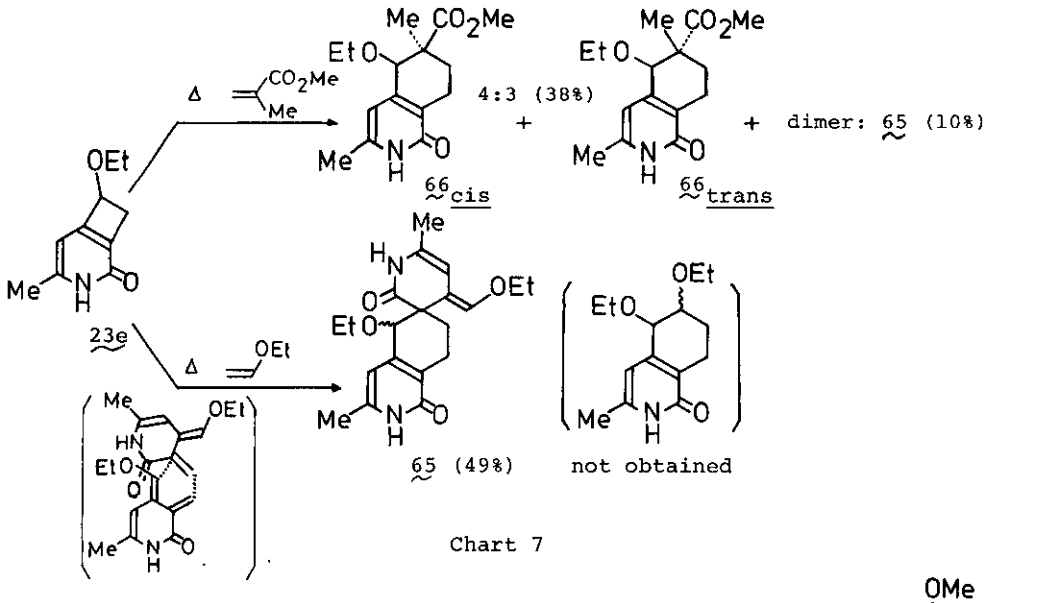
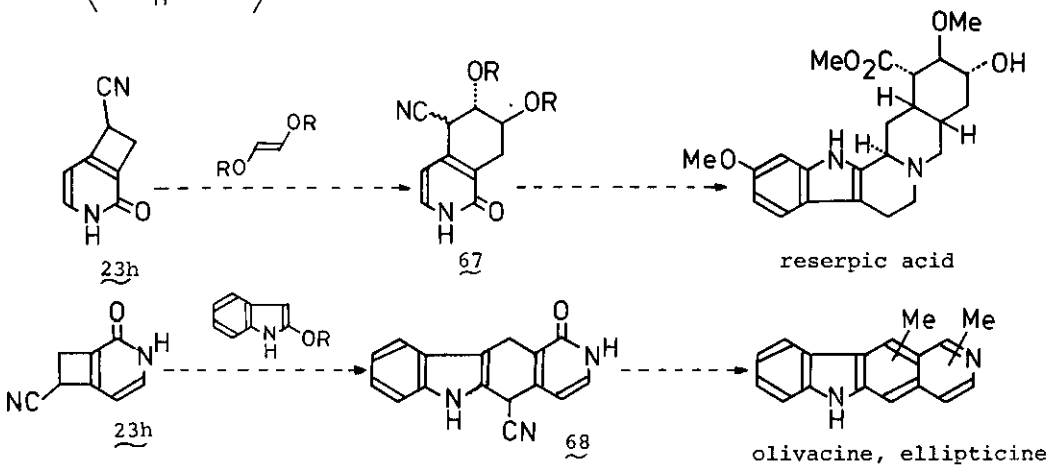
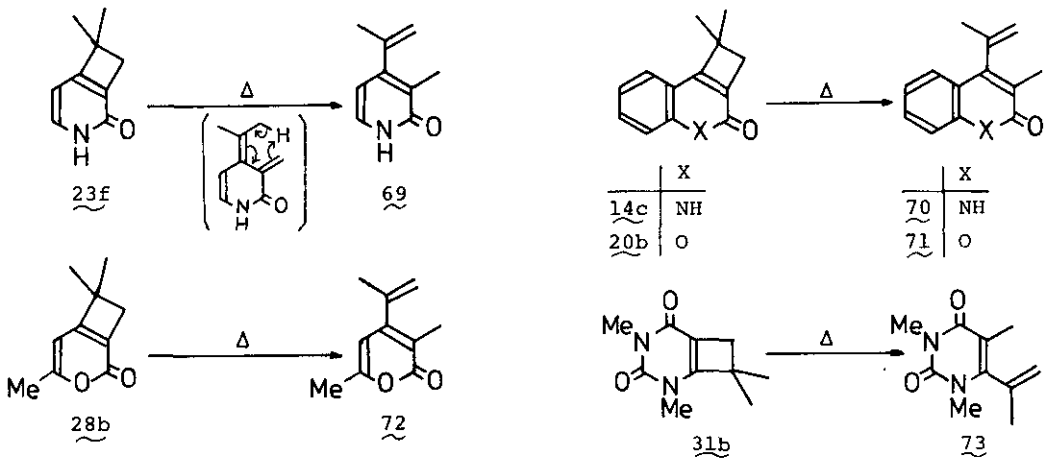

Me CO2Me
EtO
4:3 (38%)
+ dimer: 65 (10%)
66 cis
66 trans
23e
OEt
65 (49%)
not obtained

Chart 7


CN
OR
RO
NC
MeO2C
OMe
OH
MeO
23h
67
reserpic acid
NC
68
olivacine, ellipticine

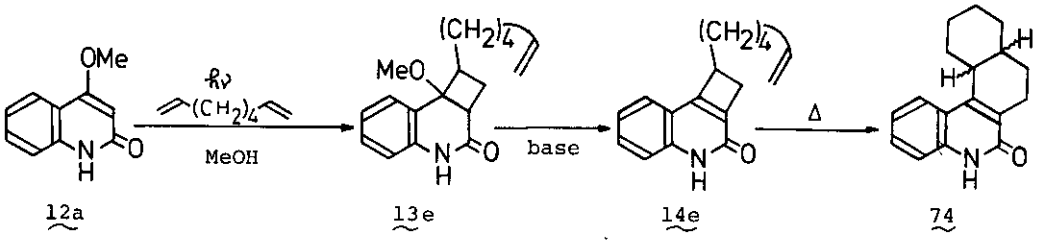
The above results showed clearly that these cyclobutane-fused heteroaromatics reacted with olefins in the same manner as benzocyclobutenes. A similarity of reactions between benzocyclobutenes and their heterocyclic analogues was further demonstrated by the following intramolecular rearrangement reactions. Thus, heating of 1,1-dimethyl-1,2-dihydrocyclobuta[c]quinolin-3(4H)-one under a comparable condition as the above cycloaddition reactions afforded 4-isopropenyl-3-methyl-2-quinolone (70) in a quantitative yield.[22] The same kind of isomerization reactions of 1,1-dialkylated benzocyclobutenes was reported by Kametani et al. and they proposed the mechanism involving an initial opening to o-quinodimethane species and subsequent [1,5]-sigmatropic hydrogen shift.[48] In the same manner, the corresponding derivatives (69,[30] 71,[29] 72,[30] and 73[49]) were obtained from respective 1,1-dimethylcyclobutenes.



III. INTRAMOLECULAR CYCLOADDITION REACTIONS OF SIX-MEMBERED HETEROCYCLIC o-DIQUINOMETHANE (GENERATED in situ FROM THE CORRESPONDING CYCLOBUTANE-FUSED HETEROAROMATICS):

As stated briefly in the foregoing section, cycloaddition reaction of 1,2-dihydrocyclobuta[c]quinolin-3(4H)-ones with electron-rich olefins suffered from longer reaction time and low yields of the cycloadducts. However, if these two functions are suitably located each other in a molecule, the adduct is formed in almost quantitative yield. It is surely due to the entropy assistance which is now well documented in the intramolecular cycloaddition reactions of benzocyclobutenes.[15,16,50] Thus, 1-(5-hexenyl)-1,2-dihydrocyclobuta[c]quinolin-3-one (14e), obtained from 12a according to our two-step procedure in 96% overall yield, af-

forded a single crystalline compound (74) in a quantitative yield by heating in o-dichlorobenzene.[22]



Since 1H-pyrano[3,4-c]pyridine nucleus is found in a series of alkaloids isolated from various Gentiana species[51] and also constitutes a common terpenoid unit of some indole and related alkaloids (e.g., ajmalicine, camptothecin, etc.), we planned a short-step synthesis of 1H-pyrano[3,4-c]pyridin-8(7H)-one (76) by utilyzing the intramolecular cycloaddition reaction of the 2-pyridone-3,4-diquinomethane derived from 1-formyl-1,2-dihydrocyclobuta[c]pyridin-3(4H)-one (75). By the route as shown in Chart 8, we have succeeded to accomplish this synthesis.[36]

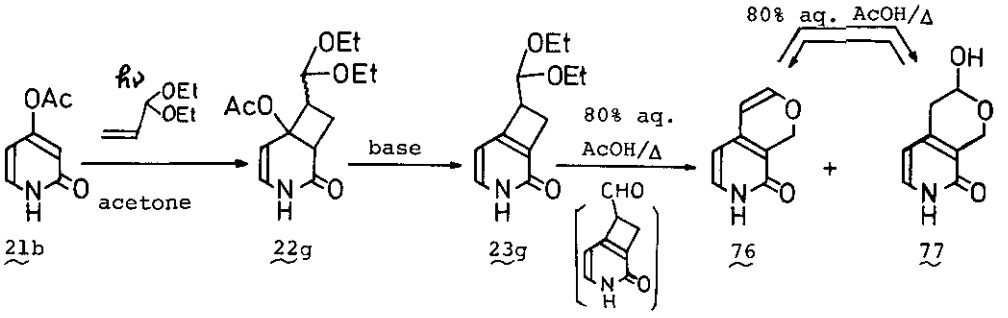
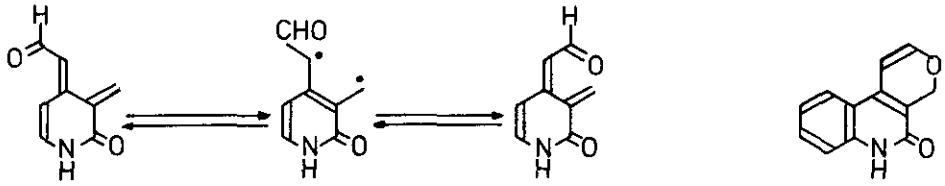


Chart 8

The accomplished method provides two synthetically useful informations. 1) Use of the diethylacetal instead of acrolein has two advantages. First, use of the former in the photoaddition reaction afforded the desired adduct (22g) almost selectively and the undesired adduct (24-type) was formed only as a minor one. Second, if the latter was used in the photoaddition step, photochemical self-polymerization of the enone occurred appreciably and the polymer prevented even the isolation of the 2+2 adduct. As noted in the previous section, the 2+2 photoaddition of 21 to electron-deficient olefins proceeds much slower than that to electron-rich olefins. 2) Since the desired product (76) can only be formed via the

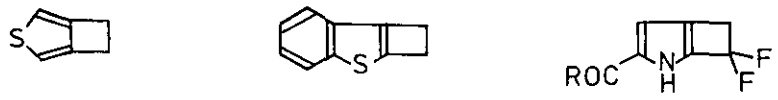
diquinomethane having Z-form, it is clear that though the E-form may probably be formed as the primary product from 75 it can equilibrates with the Z-form (78-Z) through the biradical (79). Generality of the synthetic method shown in Chart 8 has been provided with the syntheses of 6-methyl derivative of 76 and the corresponding quinolone derivatives (e.g., 80).[36] Essentially the same conversions as that from 75 to 76 have been reported in the corresponding benzocyclobutene series.[50,52-54]



78-E 79 78-Z 80

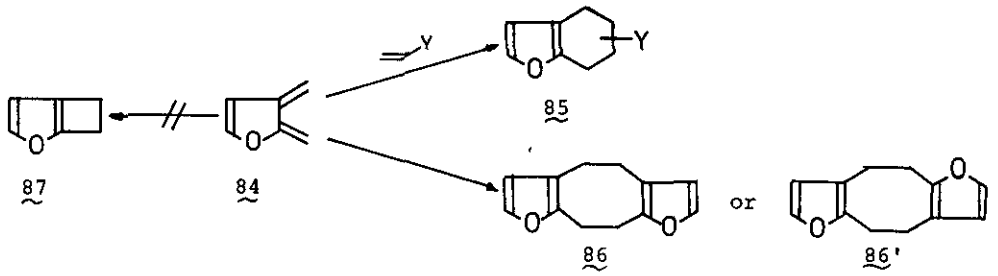
IV. OTHER POSSIBLE SOURCES OF HETEROCYCLIC o-DIQUINOMETHANE SPECIES: HETERO-ANALOGUES OF ISOTHIANAPHTHENE DIOXIDE AND CYCLOBUTANE-FUSED FIVE- AND SEVEN-MEMBERED HETEROAROMATICS:

So far, except for the syntheses of 3-thiabicyclo[3.2.0]hept-1,4-diene (1,2-dihydrocyclobuta[c]thiophene: 81)[55] and 1,2-dihydrocyclobuta[b]thiophene[56] (82), no example was reported for the synthesis of unsubstituted cyclobutane-fused heteroaromatics belonging to 5-membered heterocycles.

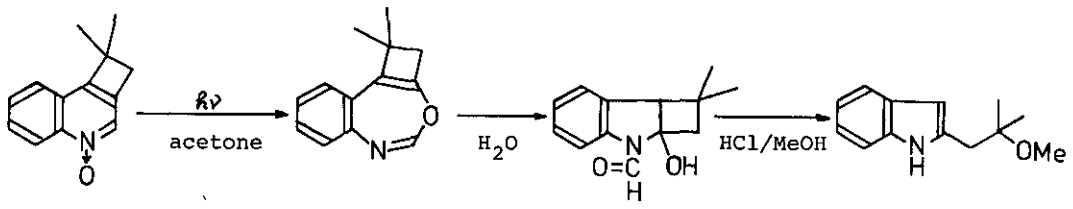


81 82 83

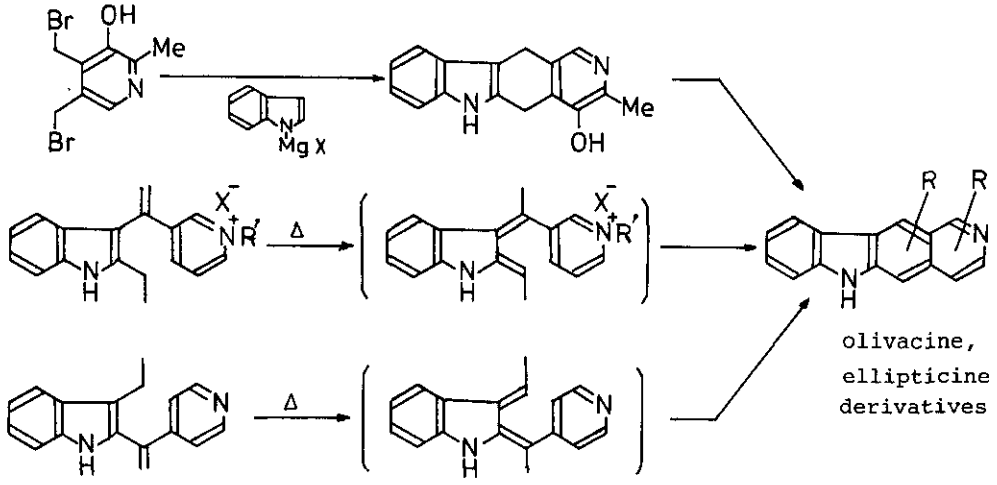
For cyclobutane-fused furan and pyrrole or their higher benzenoid homologues, there is some indication of their intrinsic instability, though some such pyrroles (83) were synthesized in very low yields (1-10%) by cyclization of the corresponding vinyl azides.[57] Thus, Trahanovsky et al. generated 2,3-dimethylene-2,3-dihydrofuran (84) from 3-methylfuryl benzoate and found that though it added to olefin in 4+2 manner or dimerized in the absence of olefin, there was no indication of the formation of 1,2-dihydrocyclobuta[b]furan (87).[58]



We also observed that attempted dehydration of 90 [obtained from the N-oxide (88) by photoisomerization[60,61] to the oxazepine (89) followed by hydrolysis] failed to give the corresponding cyclobutene derivative but to give only the ring opened indole (e.g., 91).[59]



Recently, a variety of routes to the generation of indole 2,3-diquinomethane species not using cyclobutane-fused indoles as the precursor have been explored and successfully utilized in alkaloid synthesis. Several examples are shown in Chart 9.[62-66] In any case, there is no indication of the formation of 1,2-dihydrocyclobuta[b]indole derivatives.



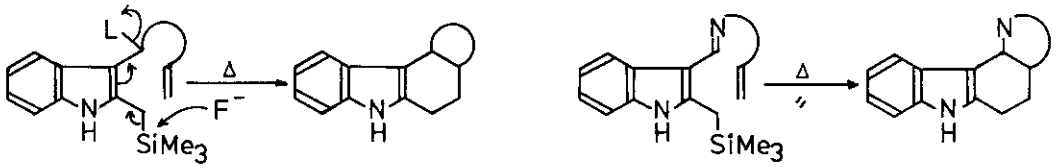
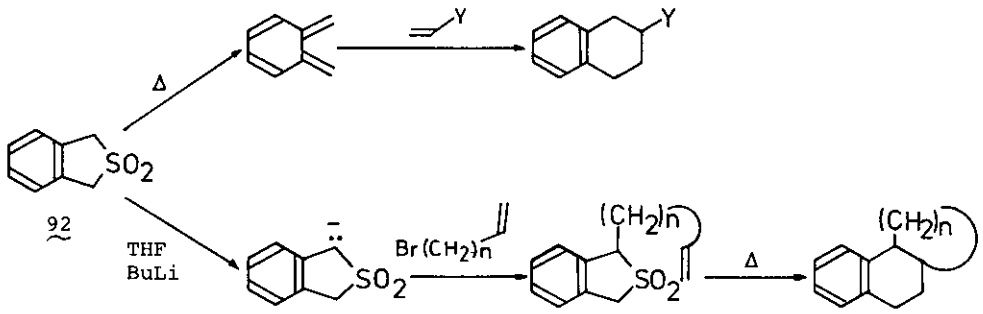
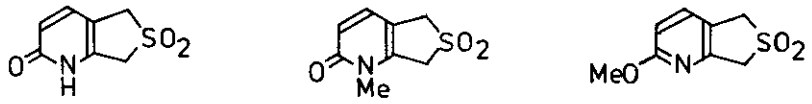


Chart 9

While in most cases, benzocyclobutenes are used as precursors of o-diquinomethanes in the carbocyclic series, isothianaphthene dioxide (92) has recently aroused interest as functionalizable masked o-quinodimethanes, which via cheletropic SO_2 extrusion to afford the quinodimethanes.[67] The advantage of using the sulfone as potential quinodimethanes is due to the ease of introduction of a variety of functional side-chain on its 1-position, thus affording various olefinic sulfone suitable for further intramolecular cyclization reactions.[50]

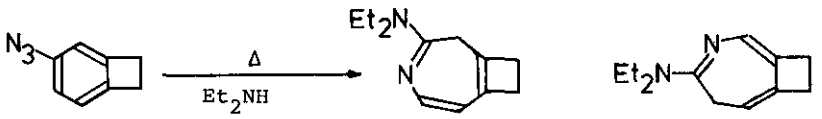


So far, only 1,3-dihydro-5-hydroxythieno[3,4-b]pyridine S,S-dioxide and its derivatives (93-95) have been synthesized as heterocyclic analogues of the isothianaphthene dioxide, but their chemical reactions have not been explored as yet.[68]



93 94 95

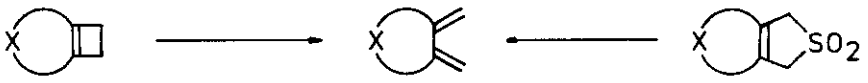
Carde and Jones obtained cyclobutane-annelated azepines by photolysis of dihydrocyclobutaphenyl azides in diethylamine, but again no reaction has been reported on these azepines.[69]



major 96 minor 97

CONCLUSION

Magnus in his recent report[65] stated the following: "Many methods have been devised for the practical generation of so-called ortho-xylylene or quinodimethane intermediates (100), but they all suffer from not being readily, or indeed if at all, applicable to heteroaromatic systems (Chart 10). The benzocyclobutene method (98) when extended to heteroaromatic compounds such as pyridine, furan, thiophene, pyrrole and indole would necessiate the synthesis of a 4-membered ring fused to these heterocycles; a formidable task in itself, and when further combined with the regiochemical problems of either intermolecular or intramolecular cyclo-addition reactions, it is hardly surprising that to date there are no examples where heterocyclic diquinomethane intermediates have been used for the synthesis of natural products. The same considerations apply to construction and utilization of sulfone precursors (99) of diquinomethane intermediates (100) derived from heterocyclic systems.



98 100 99

Chrat 10

As stated in the present review, fusion of a four-membered ring in these hetero-cycles has now become easy, so far as the six-membered heterocycles are concerned (e.g., pyridine, quinoline, isoquinoline, pyrone, coumarin, uracil). Also, most of the fundamental regiochemical problems concerning with 4+2 cycloaddition reactions (both intra- and intermolecular reactions) between these hetero-analogues of o-quinodimethane and olefin have been clarified by our recent works. So it seems possible from now that synthesis of polycyclic compounds with one heteroaromatic system and natural products can be carried out by the utilization of these cyclo-

butane-fused six-membered heteroaromatics, just like as benzocyclobutenes have been used in the synthesis of complex carbocyclic and natural compounds.

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