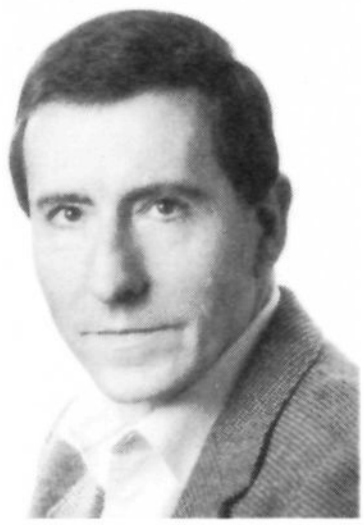
Indolo-2,3-quinodimethanes and Stable Cyclic Analogues for Regio- and Stereocontrolled Syntheses of [*b*]-Anelated Indoles

ULF PINDUR* and HOUSHANG ERFANIAN-ABDOUST

Department of Chemistry and Pharmacy, University of Mainz, D-6500 Mainz, Federal Republic of Germany

Received September 6, 1988 (Revised Manuscript Received May 24, 1989)

Contents

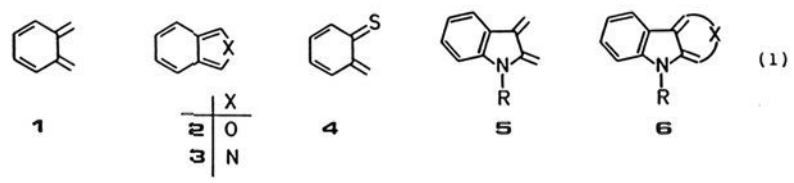


Ulf Pindur was born in 1943 in Bad Darkau, Germany. He studied at the University of Marburg (FRG), where he received his Diplom degree in pharmacy and food chemistry, his doctoral degree in synthetic organic chemistry (1974), and his Habilitation in pharmaceutical chemistry (1980). In 1980 he became Privat-Dozent at the University of Marburg and, in the same year, professor of pharmaceutical chemistry at the University of Würzburg. He was appointed professor of pharmaceutical chemistry at the University of Mainz in 1985. His current research interests include synthetic and mechanistic aspects of indole functionalization and regio- and stereocontrolled anelations of the indole skeleton, including the synthesis of indole and carbazole alkaloids. A further field of interest is the mechanistic study of color reactions in drug analysis.

Houshang Erfanian-Abdoust was born in 1959 in Teheran, Iran. He studied pharmacy at the University of Würzburg (FRG), where he received his Diplom degree. He is now working as a scientific staff member of the Department of Organic Pharmaceutical Chemistry in the Faculty of Chemistry and Pharmacy of the University of Mainz (FRG). His research interests include Diels–Alder reactions of stable cyclic indolo-2,3-quinodimethane analogues for the construction of pharmaceutically active lead substances.

I. Introduction

The utilization of *o*-quinodimethane intermediates such as **1** and their respective derivatives as enophiles for the regio- and stereocontrolled anelation of aromatic systems is of practical importance and has been applied in efficient syntheses of alkaloids, steroids, and terpenes.[1] Structurally related 8π-reaction systems such



(1)

as, for example, the isobenzofurans **2**[2] or the 2*H*-isoindoles **3**[3a] and numerous other heteroaromatic *o*-quinodimethanes[3b] have also proved to be synthetically attractive dienes in Diels–Alder reactions. Recently, the thio analogue **4** of **1** was generated in situ and successfully employed in the synthesis of anelated S-heterocycles.[4] Extension of *o*-quinodimethane chemistry to include the 2,3-bis(methylene)-2,3-dihydroindole system **5** and its cyclic analogues **6** is also of major synthetic interest. For example, many polycyclic organic compounds containing the indole or carbazole nucleus possess important pharmacological properties and have been target compounds for synthesis.[5] Hence, the development of the heteroaromatic *o*-quinodimethane/Diels–Alder methodology for the regio- and stereocontrolled syntheses of polycyclic indoles and pharmacologically active derivatives would provide a highly attractive approach to this class of compounds. Thus, a major objective of the present review is to present for the first time the scope and limitations of inter- and intramolecular [$_{\pi}$4s + $_{\pi}$2s]-cycloaddition reactions of in situ generated indolo-2,3-quinodimethanes [2,3-bis(methylene)-2,3-dihydroindoles] **5** and their stable cyclic analogues **6**. Literature published up to the start of 1989 has been covered.

0009-2665/89/0789-1681$06.50/0

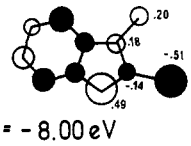
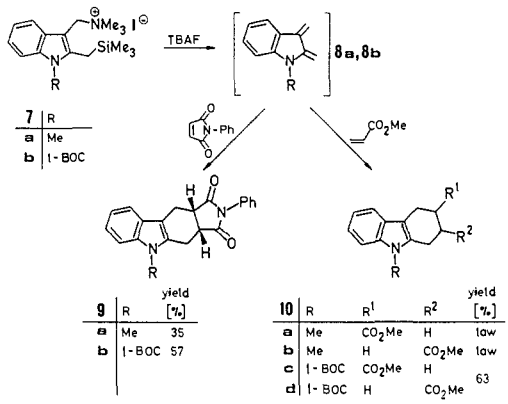


Figure 1. HOMO of indolo-2,3-quinodimethane according to MNDO calculations.[6a]

SCHEME 1

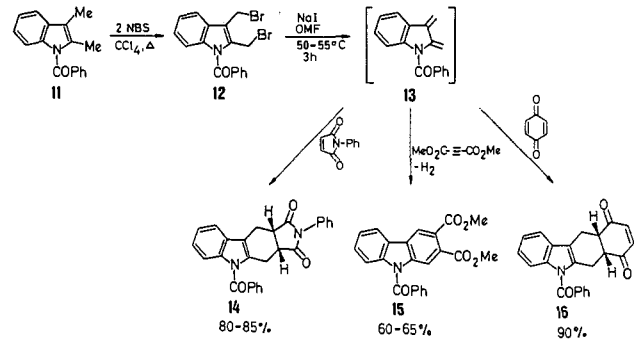


The heterocyclic diene reactivity of **5** and **6** is primarily determined by the 2-aminobutadiene structural unit. Our MNDO calculations on the parent compound **5** (R = H; Figure 1)[6a] have shown that the [$_\pi$4s + $_\pi$2s]-cycloaddition reactions with electron-poor dienophiles are $HOMO_{diene}$–$LUMO_{dienophile}$ controlled processes and that the peri- and regioselectivities found in numerous experimental syntheses can be predicted satisfactorily from the HOMO topologies of **5** or **6**.[6] Most of the reactions of **5** and **6** and their applications in Diels–Alder reactions described here are based on well-known concepts of *o*-quinodimethane chemistry.[1] The results clearly demonstrate that, in comparison with other processes, the *indolo-2,3-quinodimethane/Diels–Alder methodology* represents the shortest and most elegant method for the preparation of selectively functionalized [*b*]-anelated indoles (including indole alkaloids and carbazoles).

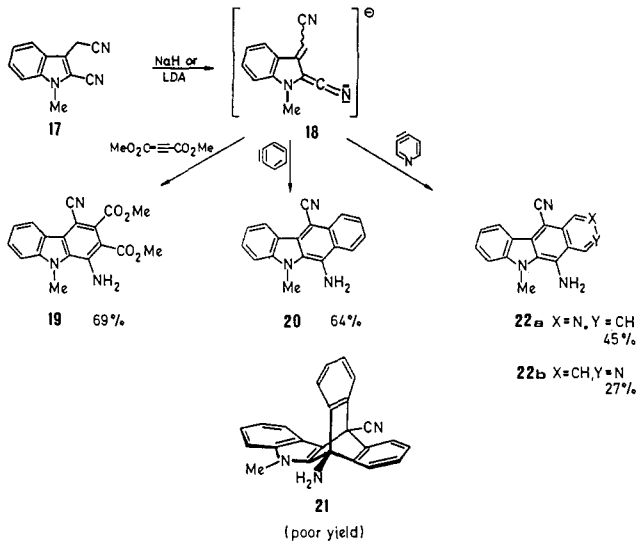
II. Generation of Reactive Indolo-2,3-quinodimethanes by 1,4-Elimination and Synthetic Applications in Diels–Alder Reactions

N-Protected 2,3-disubstituted indoles are generally used as precursors for the in situ generation of indolo-2,3-quinodimethanes of the type **5** since, from a structural point of view, they are susceptible to selective 1,4-eliminations. Thus, *N*-methyl- and *N*-(*tert*-butoxycarbonyl)indolo-2,3-quinodimethanes **8a,b** can be generated easily from the silylated indolylammonium salts **7a,b** by fluoride ion induced 1,4-eliminations.[7] The salts **7** are accessible from the corresponding N-protected 2-methylindoles by way of Mannich reactions, selective lithiation of the indole 2-methyl groups, subsequent silylation, and quaternization. The indolo-2,3-quinodimethanes **8a,b** generated in situ are trapped with *N*-phenylmaleimide or methyl acrylate to furnish the carbazole derivatives **9** or **10**, respectively. The intermediate **8b** in particular also undergoes dimerization to form spiro compounds. In comparison with **8a**, the cycloaddition of **8b** with methyl acrylate proceeds with higher regioselectivity (major isomer: **10d**) (Scheme 1).

SCHEME 2



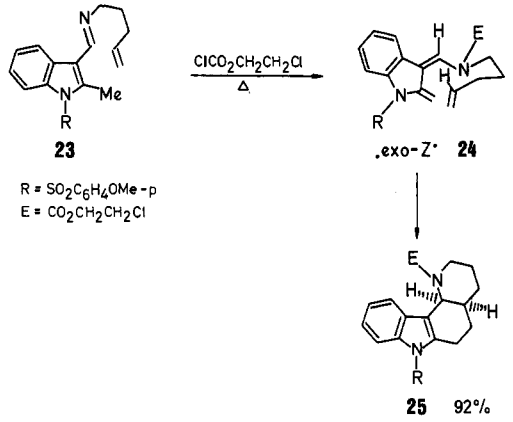
SCHEME 3



A simplified route to an N-protected indolo-2,3-quinodimethane starts from *N*-benzoyl-2,3-dimethylindole (**11**)[8] and involves an iodide ion induced 1,4-elimination. Radical side-chain bromination of **11** with *N*-bromosuccinimide gives rise to *N*-benzoyl-2,3-bis(bromomethyl)indole (**12**). When the latter is treated with sodium iodide in dimethylformamide at 50–55 °C and then allowed to react with CC dienophiles (e.g., *N*-phenylmaleimide, dimethyl acetylenedicarboxylate, and 1,4-benzoquinone), the novel, selectively functionalized carbazole derivatives **14**, **15**, and **16**, respectively, are obtained via the generated intermediate **13** (Scheme 2).

Anionic indolo-2,3-quinodimethanes exhibit a particularly pronounced enophile reactivity as a result of the increased HOMO energy level and/or the increase in the net atomic charge.[6b] By means of the interesting sequence "3-acylindole/diethyl phosphorocyanidate [$(EtO)_2P(O)CN$]", 2-cyanoindole-3-acetonitriles can be prepared,[9] which, in the presence of a strong base, smoothly give rise to indolo-2,3-quinodimethane anions. This strategy has been used for the selective synthesis of aminocarbazoles.[9] As illustrated in Scheme 3, reaction of **17** with dimethyl acetylenedicarboxylate in the presence of sodium hydride gives rise to the polyfunctionalized carbazole **19**, reaction of **17** with lithium diisopropylamide (LDA) in the presence of benzyne produces compounds **20** and **21** via single and double Diels–Alder reactions, and reaction with 3,4-pyridyne

SCHEME 4



(generated from 3-chloropyridine and LDA) furnishes the pyrido[*b*]anelated carbazoles **22a,b** in the same manner (Scheme 3).

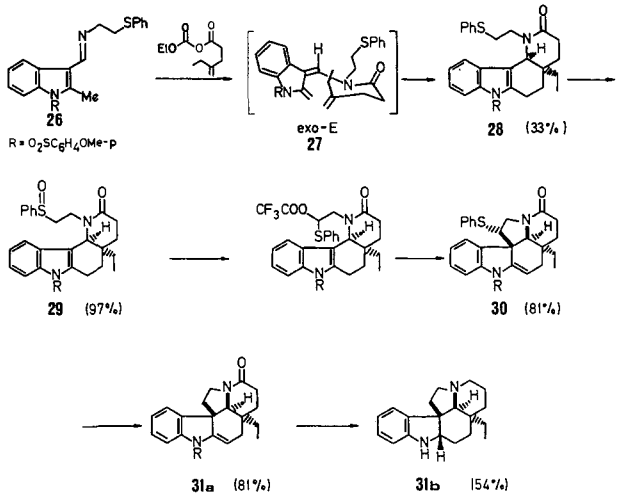
An in situ indolo-2,3-quinodimethane strategy has also been used with 2-alkyl-3-vinylindoles[10] or 3-alkyl-2-vinylindoles[11] to form, via a thermally induced [1,5]-sigmatropic shift and electrocyclization, 5*H*-benzo[*b*]carbazoles or pyrido[4,3-*b*]carbazoles (e.g., ellipticine[25]), respectively.

III. Intramolecular [4 + 2]-Trapping Reactions of Generated Indolo-2,3-quinodimethanes To Form Penta- and Heptacyclic Indole Alkaloids

A highly convergent and elegant reaction sequence for the preparation of indole alkaloids possessing several stereocenters, especially those of the *Aspidosperma* and *Kopsane* types, was first realized by Magnus and coworkers.[12-17] The scope and limitations, including mechanistic aspects, of this route have been studied systematically, and a series of pharmacologically interesting indole alkaloids were synthesized under high regio- and stereocontrol through intramolecular trapping of an in situ generated indolo-2,3-quinodimethane. As a model reaction for this strategy, a stereocontrolled cyclization of the indolylimine **23** to form the tetracyclic product **25**[14] will be discussed first (Scheme 4). Starting from **23** in the presence of a chloroformate (e.g., $ClCO_2CH_2CH_2Cl$), the indolo-2,3-quinodimethane **24** was generated and underwent stereoselective cyclization to yield the cis cycloadduct **25** (Scheme 4).

This highly stereoselective syntheses of **25** can be correlated with either the exo-*Z* (**24**) or endo-*E* transition states. The concept was developed further to provide a successful total synthesis of *Aspidosperma*-type alkaloids.[14] A six-step total synthesis of (±)-aspidospermidine via the "endocyclic amide route"[17] (Scheme 5) starts, for example, from **26**, which, on treatment with the mixed anhydride derived from 4-ethylpent-4-enoic acid in chlorobenzene at 140 °C for 2.75 h, was converted to **28** via the intermediate **27**. Oxidation of **28** with *m*-chloroperoxybenzoic acid (MCPBA) at 0 °C gave the sulfoxide **29** as a mixture of diastereomers. When this sulfoxide was treated with trifluoroacetic anhydride (TFAA) at 0 °C followed by rapid heating to 130 °C (addition of chlorobenzene), the pentacyclic compound **30** was formed via an intramolecular Pummerer-type reaction. Desulfurization of **30** (Raney nickel) followed by $LiAlH_4$ reduction furnished,

SCHEME 5. Endocyclic Amide Route to (±)-Aspidospermidine

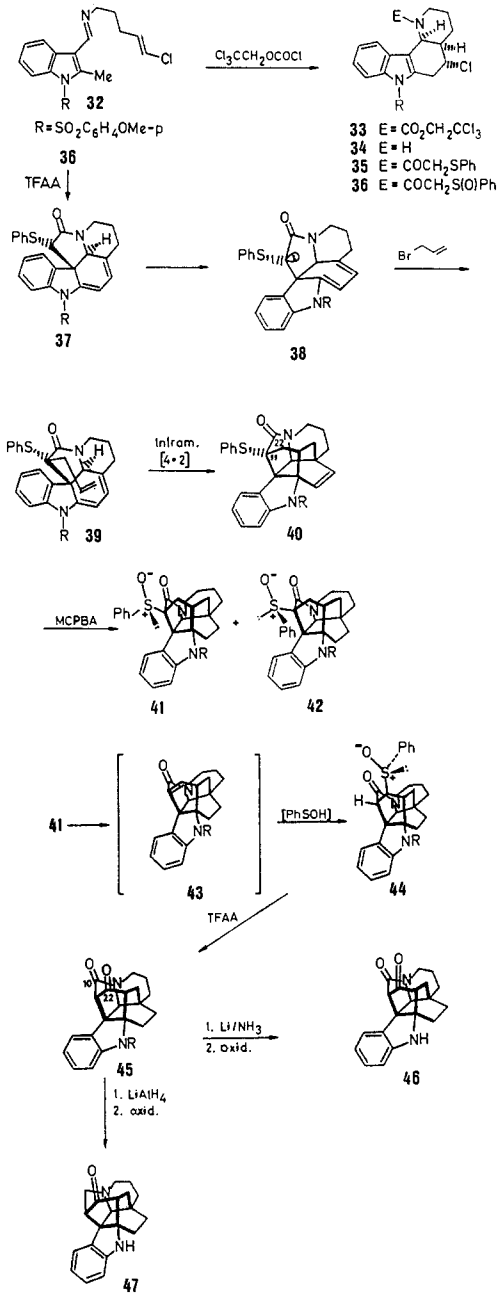


via compound **31a**, (±)-aspidospermidine (**31b**) in an overall yield of 11.7%.[14,17]

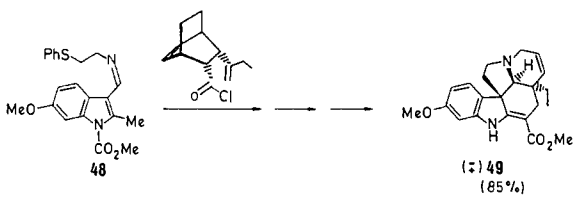
Following the same convergent strategy, the total syntheses of the indole alkaloids (±)-10,22-dioxokopsane (**46**) and (±)-kopsane (**47**) (Scheme 6) were achieved and the mechanisms were also investigated.[15] The imine **32** was condensed with 2,2,2-trichloroethyl carbonochloridate to give the tetracyclic carbamate **33**. Removal of the carbamate protecting group with zinc in acetic acid furnished the secondary amine **34**. This amine was converted into the sulfoxide **36** by treatment with (phenylthio)acetyl chloride and subsequent oxidation of **35**. The sulfoxide **36** was transformed directly into the homoannular diene **37** by treatment with TFAA in chlorobenzene at 135 °C. The crucial allylation of the C-11 carbanion **38**, derived from **37** by treatment with lithium hexamethyldisilazide, gave exclusively the desired endo-allyl product **39**. In the chiral series,[15] the allylation at C-11 takes place with retention of configuration. Heating of **39** at 100 °C gave compound **40** possessing the basic kopsane skeleton. The oxidation level at C-11 was transferred to C-22 by elimination of the sulfoxide function from **41** to give **44** via the anti-Bredt compound **43**. Treatment of **44** with TFAA furnished *N*-[(*p*-methoxyphenyl)sulfonyl]-10,22-dioxokopsane (**45**). Conversion of **45** into **46** or **47**, respectively, was achieved by reduction with Li/NH_3 and oxidation to give **46** or reduction of **45** with $LiAlH_4$ and subsequent oxidation to form **47**. The synthesis proceeds through 14 steps in an overall yield of 5.8% (Scheme 6).

The most recent advance in this strategy has been the use of an enantiomerically pure norbornene derivative as a chiral auxiliary agent in an enantio- and stereospecific version of the intramolecular indolo-2,3-quinodimethane cyclization.[16] This work also demonstrates the suitability of the present methodology for the syntheses of enantiomerically pure 16-methoxy-substituted *Aspidosperma*-type alkaloids. For the synthesis of (+)- or (−)-16-methoxytabersonine (Scheme 7), the 6-methoxyindole derivative **48** was acylated at the imine function with a chiral [(+) or (−) enantiomer] norbornenoyl chloride. The resultant norbornenylacyl derivative rearranged to an indolo-2,3-quinodimethane which underwent intramolecular cyclization stereospecifically. An intramolecular Pummerer reaction with

SCHEME 6



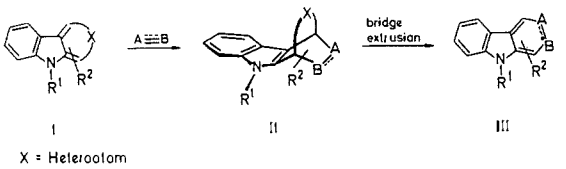
SCHEME 7



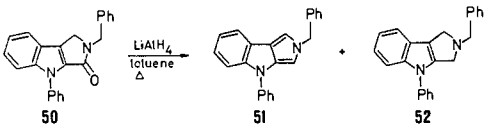
a subsequent retro-Diels–Alder step and further selective functional group transformations gave rise to either (+)- or (−)-16-methoxytabersonine (**49**), depending on the use of the (+) or (−) form of the acylating auxiliary agent [use of the (−) reagent yields the (+) form of **49**], in about 85% yield (Scheme 7).

By employing a related "indolo-2,3-quinodimethane/intramolecular Diels–Alder (IMDA) reaction" strategy, Herslöf and Martin prepared the novel, conformationally fixed *trans*-serotonine homologue 7-[(*p*-methoxyphenyl)sulfonyl]-3-methyl-1,2,3,4,4a,5,6,11c-

SCHEME 8



SCHEME 9



octahydro-7*H*-pyrido[3,4-*c*]carbazole in 58% yield via the intramolecular trapping of an indolo-2,3-quinodimethane as a diene–dienophile system.[18]

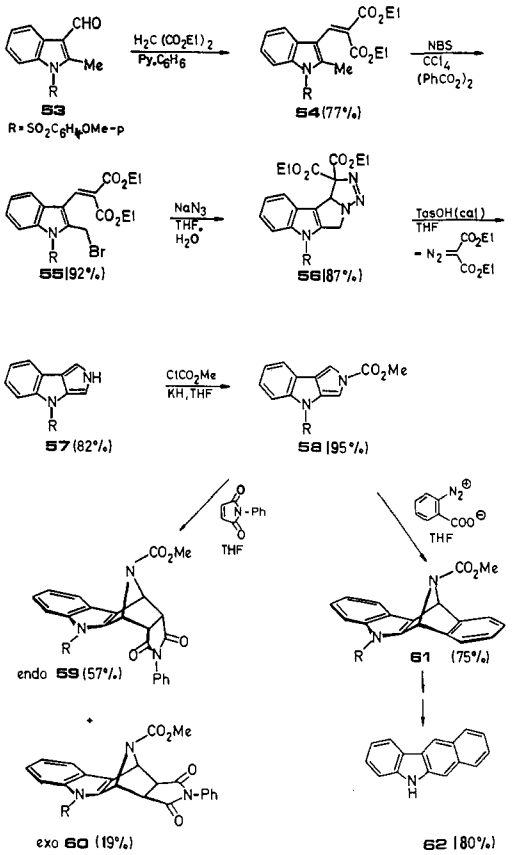
IV. Stable Cyclic Analogues of Indolo-2,3-quinodimethanes in Diels–Alder Reactions

The stable cyclic analogues I of the indolo-2,3-quinodimethanes are particularly versatile dienes for Diels–Alder reactions. In these cases the 2,3-bis(methylene)-2,3-dihydroindole structure is stabilized by the presence of a heteroatom capable of conjugation in the ring. Even so, such compounds are still reactive and afford cycloadducts useful for subsequent transformations. In accord with the "Diels–Alder/bridge extrusion methodology", they react initially with dienophiles to form the bridged adducts II. In many cases, selectively functionalized carbazoles or [*b*]-anelated indoles of the general type III can be obtained by removal of the bridging unit (Scheme 8).

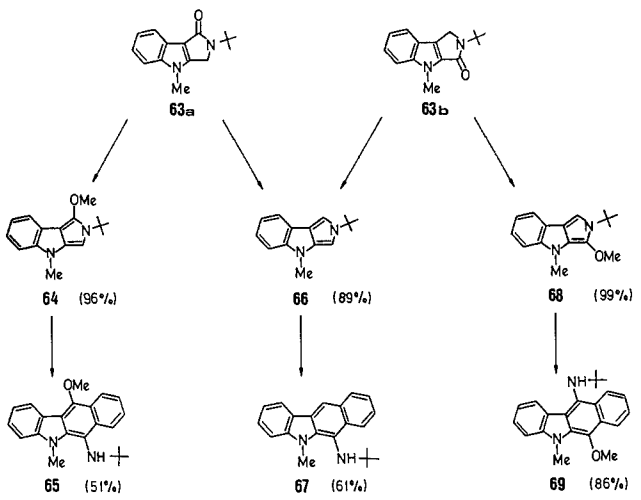
The first synthesis leading to a 2,4-dihydropyrrolo[3,4-*b*]indole as an indolo-2,3-quinodimethane analogue was described in ref 19 (Scheme 9). 2-Benzyl-4-phenylpyrrolo[3,4-*b*]indol-3(2*H*)-one (**50**) was used as the starting material for the preparation of the mentioned 2-benzyl-4-phenyl derivative **51**. Reduction of **50** with $LiAlH_4$ gave **51** in addition to **52** as a further product (yield of each: approximately 35%). A mechanism was discussed and used to explain the failure of analogous reactions with N-unsubstituted indoles corresponding to **50**.

A further variation proceeds through a regiocontrolled [*b*]-anelation of the indole skeleton.[20] For the synthesis of 2-(methoxycarbonyl)-4-[(*p*-methoxyphenyl)-sulfonyl]-2,4-dihydropyrrolo[3,4-*b*]indole (**58**) (Scheme 10), the indole-3-carbaldehyde **53** was initially condensed with diethyl malonate in a Knoevenagel reaction to give **54**. Selective side-chain bromination with NBS furnished **55**, which, on treatment with NaN_3, underwent cyclization via an intramolecular 1,3-dipolar cycloaddition to yield the triazoline **56**. Under proton catalysis, the tetracyclic compound **56** was cleaved in a 1,3-dipolar cycloreversion process to form 2,4-dihydropyrrolo[3,4-*b*]indole (**57**). On treatment with methyl carbonochloridate, **57** was converted to the air-stable *N*-methoxycarbonyl derivative **58**. Under reflux conditions in THF, the heterocyclic diene **58** took part in Diels–Alder reactions with, e.g., *N*-phenylmaleimide or arynes to give the products **59**, **60**, or **61**. The N bridge in **61** was reductively cleaved with lith-

SCHEME 10



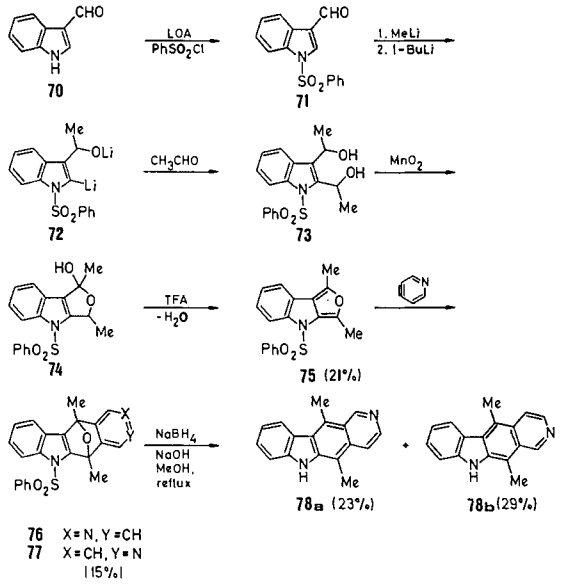
SCHEME 11



ium/liquid ammonia (reductive extrusion of the N bridge), resulting in the formation of 6,11-dihydro-5*H*-benzo[*b*]carbazole, which, in turn, was smoothly dehydrogenated on treatment with DDQ to furnish 5*H*-benzo[*b*]carbazole (**62**) in 80% yield (Scheme 10).[21]

2-*tert*-Butyl-4-methyl-2,4-dihydropyrrolo[3,4-*b*]indole (**66**) has been prepared previously via selective reduction of 2-*tert*-butyl-4-methyl-2,4-dihydropyrrolo[3,4-*b*]indol-1(2*H*)-one (**63a**) or -3(2*H*)-one (**63b**) with diisobutylaluminum hydride (DIBAH) (Scheme 11).[22] The same precursors **63a** and **63b** were transformed into the 2-*tert*-butyl-4-methyl-2,4-dihydro[3,4-*b*]indoles **64** and **68** bearing a methoxy group in the 1- or 3-position, respectively, via a two-step procedure comprising O-alkylation and CH deprotonation. The novel cyclic indolo-2,3-quinodimethane analogues **64**, **66**, and **68** also

SCHEME 12

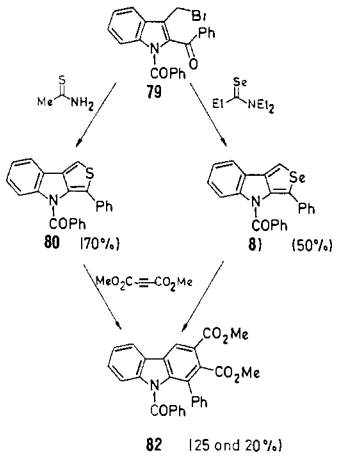


react as heterocyclic dienes with, e.g., aryne (generated from 1,2-dibromobenzene and methyllithium in THF under an argon atmosphere) via the bridged and, as a result of the ring strain, kinetically unstable cycloadducts through selective ring opening at the imino bridge to give the substituted 5*H*-benzo[*b*]carbazoles **65**, **67**, and **69** readily (Scheme 11).

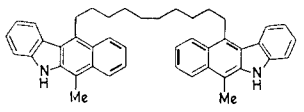
4*H*-Furo[3,4-*b*]indoles can also be employed successfully for the regiocontrolled [*b*]-anelation of the indole skeleton.[23-26] The Diels–Alder reactivity of this substance class with benzyne, 3,4-pyridyne, *N*-phenylmaleimide, and dimethyl acetylenedicarboxylate has been investigated in detail.[23,24] This new annulation strategy was also used to produce the cytostatically active alkaloids ellipticine and isoellipticine (Scheme 12).[24,25] For this purpose, 1,3-dimethyl-4-(phenylsulfonyl)-4*H*-furo[3,4-*b*]indole (**75**) was used as starting material.[24] Compound **75** was obtained from indole-3-carbaldehyde (**70**) in a five-step sequence as follows (Scheme 12). First, the nitrogen atom of **70** was protected, and the resultant indole **71** was selectively methylated and lithiated to give **72**. Reaction of **72** with acetaldehyde gave the diol **73**, which spontaneously cyclized to the lactol **74** after selective oxidation. Trifluoroacetic acid catalyzed dehydration of **74** finally resulted in the air-stable key substance **75** in an overall yield of 21%. A similar variation[24] gave rise to the novel furanoindole **75** in 46% overall yield. The total syntheses of ellipticine and isoellipticine (Scheme 12) were realized by Diels–Alder reaction of **75** with 3,4-pyridyne (generated from 3-chloro-4-iodopyridine and *tert*-butyllithium at −100 °C). (In a further variation, 3,4-pyridyne was successfully generated by lead acetate oxidation of the precursor 1-aminotriazolo[4,5-*c*]-pyridine.) This gave rise to an isomeric mixture of the Diels–Alder adducts **76** and **77**. The oxygen bridge and the N-protecting group were removed by treatment with $NaBH_4$ and NaOH. Workup by flash chromatography allowed the isolation of ellipticine (**78a**) in 23% yield and isoellipticine (**78b**) in 29% yield (Scheme 12).

Following an analogous strategy, a new, potential bifunctional nucleic acid intercalating agent, namely, 1,10-bis(6-methyl-5*H*-benzo[*b*]carbazol-11-yl)decane (**78c**), was synthesized.[26] The construction of **78c** pro-

SCHEME 13



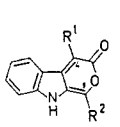
ceeds via a double Diels–Alder reaction of the corresponding bis(furo[3,4-*b*]indole) derivative.



78c (55%, last step) (12)

Starting from selectively functionalized indolyl ketones, a series of substituted thieno[3,4-*b*]indoles and substituted selenolo[3,4-*b*]indoles, both representing new classes of heterocycles, were prepared.[27] Thus, for example, the reactions of the trifunctionalized indole **79** with thioacetamide or *N,N*-diethylselenopropanamide give rise to the tricyclic products **80** or **81**, respectively (Scheme 13). The [4 + 2]-cycloaddition reactions of these thermally stable compounds with dimethyl acetylenedicarboxylate lead directly to the dimethyl carbazoledicarboxylate **82**. This reaction result also provides indirect evidence for the structures of the two heterocyclic dienes **80** and **81** (Scheme 13).

Pyrano[3,4-*b*]indol-3-ones **83** represent one of the most interesting and preparatively accessible cyclic synthetic equivalents of indolo-2,3-quinodimethane.[28]

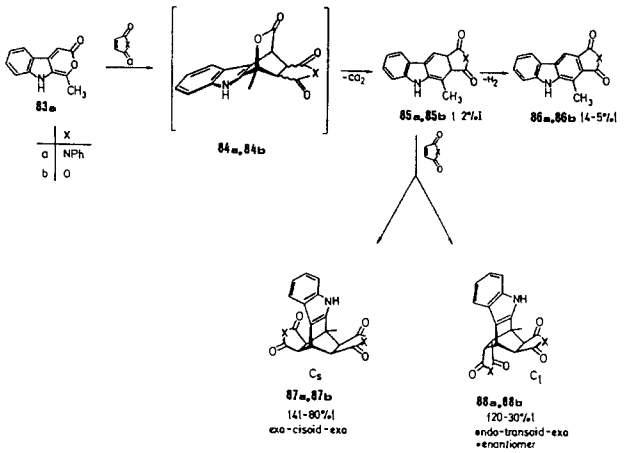


83	R^1	R^2
a	H	Me
b	Me	Me
c	H	Et
d	H	Ph
e	H	n-Prop
f	H	i-Prop
g	H	n-Bu
h	H	t-Bu
i	H	C_5H_{11}

(13)

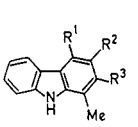
They are obtained from indole-2-acetic acid or 2-(3-indolyl)propanoic acid and acid anhydrides under BF_3 catalysis in high yields. This class of compounds was first described by Plieninger and co-workers[28] and has recently been investigated thoroughly with regard to Diels–Alder reactivity by others[29,30-32,39] and by our group.[33-35] These compounds react with dienophiles in a [4 + 2]-cycloaddition/[4 + 2]-cycloreversion (extrusion of CO_2) process to give usually selectively functionalized [*b*]-anelated indoles. Our MNDO calculations[35,36] suggest that the [$_\pi$4s + $_\pi$2s]-cycloaddition reactions of **83** are all $HOMO_{diene}$–$LUMO_{dienophile}$ controlled processes[39] and that the regiochemistries of the reactions with acceptor-substituted CC dienophiles are in good agreement with the magnitudes of the participating coefficients in the transition state as given by the FMO theory. Recently, it has also been demonstrated that a reversal of the regiochemistry in a series of cycloaddition reactions of alkynes with **83** may be brought about by steric effects (see below).[39]

SCHEME 14



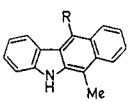
We have reinvestigated the cycloaddition reactions of **83a** with *N*-phenylmaleimide and maleic anhydride first performed by Plieninger and co-workers[28] and have now completely clarified the reaction sequence (Scheme 14).[33] By way of the primary cycloadduct **84** formed from the reaction of **83** with the two cyclic dienophiles, the [*b*]-anelated carbazole **85** and its dehydrogenation product **86** result after extrusion of CO_2.[37] The unstable carbazole derivative **85**, in addition, is trapped by a double Diels–Alder reaction with the CC dienophile present in the reaction medium and thus forms also the *exo-cisoid-exo*- and *endo-transoid-exo*-tetrahydrobarrelenes **87** and **88** which are the main products of this reaction sequence.

Compounds **83a,b** also react with numerous other CC dienophiles such as, for example, dimethyl acetylenedicarboxylate and dibenzoylacetylene to give the novel carbazoledicarboxylates **89a,b** and dibenzoylcarbazoles **89c,d**.[29] The dibenzoylcarbazoles, in turn, react with



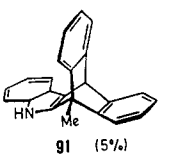
89	R^1	R^2	R^3	yield [%]
a	H	CO_2Me	CO_2Me	81
b	Me	CO_2Me	CO_2Me	67
c	H	COPh	COPh	76
d	Me	COPh	COPh	52

(14)



90	R	yield [%]
a	H	44
b	Me	31-38

(15)

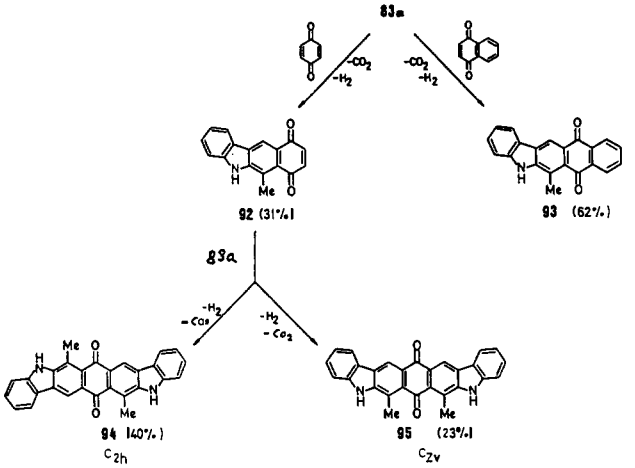


91 (5%) (16)

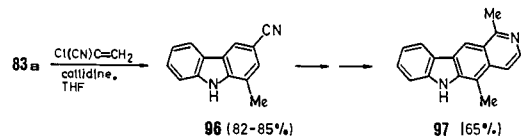
hydrazine to form pyridazo[4,5-*b*]carbazoles. The pyranoindolones **83a,b** also react with benzyne to give the benzo[*b*]carbazoles **90a,b**;[29,34] with **83a** the double Diels–Alder adduct **91** is formed additionally.[34]

The pyrano[3,4-*b*]indol-3-one (**83a**) also readily undergoes cycloaddition reactions with 1,4-benzo- and 1,4-naphthoquinones to produce the new single and double Diels–Alder adducts **92–95**[34] of the [*b*]-anelated carbazole series (Scheme 15); these compounds are ca-

SCHEME 15



SCHEME 16

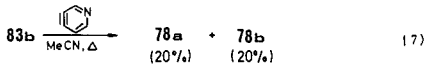


pable of intercalating DNA.[25,34]

The "cycloaddition/cycloreversion" strategy[37] with methylated pyranoindolones has also been employed in the total syntheses of pyrido[4,3-*b*]carbazole alkaloids.[25,30-32] According to ref 30, for example, **83a** reacts with 2-chloropropenenitrile in the presence of collidine as an auxiliary base to yield the 3-cyanocarbazole **96**, which, by means of Jackson's route, can easily be converted to the alkaloid olivacine (**97**) in 65% yield (Scheme 16).

Analogously, CH_2=CCl(CHO) and CH_2=CCl(OMe) also undergo regioselective cycloadditions with **83a**. The resultant 3-acceptor-substituted carbazoles can also be further transformed into pyrido[4,3-*b*]carbazoles (1-demethylolivacine, olivacine).[30]

The shortest known route to the alkaloids ellipticine (**78a**) and isoellipticine (**78b**) proceeds via a Diels–Alder reaction of **83b** with 3,4-pyridyne—generated in situ from 3-(3,3-dimethyltriazin-1-yl)pyridine-4-carboxylic acid—as the key step.[31,32] On repeating some of the



(7)

reactions cited in this review in our laboratory, we found that this interesting concept for the direct preparation of other cytostatically active pyrido[4,3-*b*]carbazoles is apparently limited to the sufficiently reactive 1,4-dimethyl derivative **83b**.[34,35] The loss of regioselectivity in the Diels–Alder reaction of **83b** with 3,4-pyridine is in good agreement with the predictions of the FMO concept (Figure 2).[6b] The LUMO coefficients in the heteroaryne are not sufficiently polarized.[6b,36]

The problem of the regiochemistry and the synthetic scope of application for the preparation of selectively functionalized carbazoles was recently investigated by us in detail for the example of the reactions of **83a** and **83b** with mono-acceptor-substituted CC dienophiles.[35] Thus, for example, we found that in the cycloaddition/cycloreversion variation with acceptor-substituted CC dienophiles (A≒B) **83a** showed poor regioselectivities whereas the 1,4-dimethyl derivative **83b**

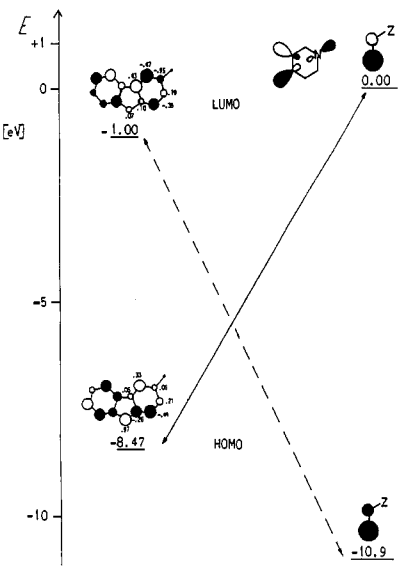
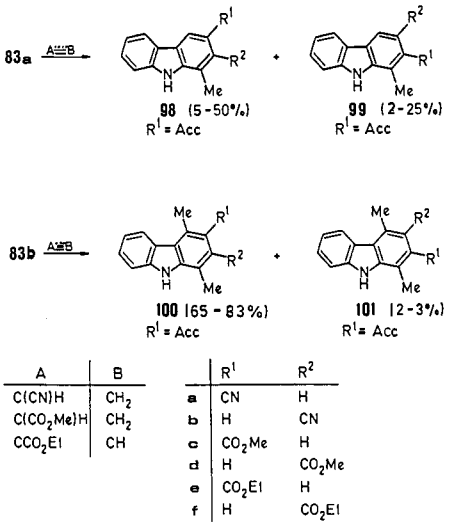


Figure 2. Prediction of the reactivity and regioselectivity of the Diels–Alder reactions of the pyrano[3,4-*b*]indol-3-one parent compound with 3,4-pyridyne and acceptor-substituted CC dienophiles (MNDO calculations).[35,36]

SCHEME 17

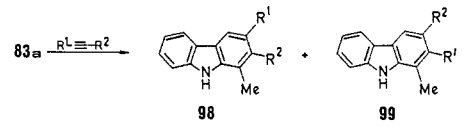


A	B
C(CN)H	CH_2
$C(CO_2Me)H$	CH_2
CCO_2Et	CH

	R^1	R^2
a	CN	H
b	H	CN
c	CO_2Me	H
d	H	CO_2Me
e	CO_2Et	H
f	H	CO_2Et

showed high regioselectivities in all cases. The 3-acceptor-substituted carbazoles **98** and **100** are the main products in most cases. Qualitative application of the FMO concept[6b] on the example of the parent compound of **83** (MNDO calculations, Figure 2) predicts the preference for the formation of 3-acceptor-substituted carbazoles in a $HOMO_{diene}$–$LUMO_{dienophile}$ controlled [$_\pi$4s + $_\pi$2s]-cycloaddition. In the poorly regioselective reactions of **83a** with the unsymmetrical CC dienophiles, different contributions of frontier orbital control and charge control[6b] as well as steric effects are apparent in dependence on the structure of the dienophile. According to the polarity concept, the 2-acceptor-substituted carbazole derivatives **99** and **101** (R^1 = Acc) are to be expected preferentially from the reactions of **83** with mono-acceptor-substituted CC dienophiles (calculation of net atomic charge of the parent compound **83**).[35,36] According to predictions of the FMO concept, as mentioned above, the 3-acceptor-substituted carbazoles **98** and **100** (R^1 = Acc) are, however, to be expected. The Diels–Alder reactions of **83b** with the dienophiles A≒B tested here are thus in good agree-

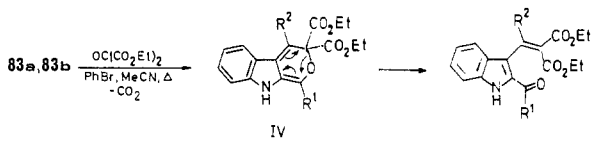
SCHEME 18



entry	R^1	R^2	products 98, 99	combined yield, %	ratio (250-MHz ^1H NMR)
1	CO_2Me	H	**g**	84	1:1
2	COPr	H	**h**	87	2.8:1
3	Ph	H	**i**	32	>20:1
4	C_5H_{11}	H	**j**	16	>20:1
5	tBu	H	**k**	8	>20:1
6	CO_2Me	Me	**l**	36	1:5
7	COPr	Me	**m**	42	1:3
8	CO_2Me	Ph	**n**	74	1:3.4
9	CO_2Me	Pr	**o**	33	1:10
10	CO_2Me	tBu	**p**	28	1:>20
11	CO_2Me	PrCH(OH)	**q**	64	1:>20[a]
12	CO_2Me	PrCO	**r**	93	1:1.2

[a] Exists as the tetracyclic lactone.

SCHEME 19



102	R^1	R^2	yield [%]
a	Me	H	25
b	Me	Me	60

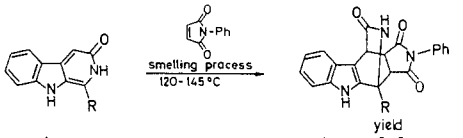
ment with a preferred frontier orbital controlled cyclization (Scheme 17).

In a recently published investigation, Moody et al.[39] reported on the regioselectivities of the Diels–Alder reactions of a series of 1-substituted pyrano[3,4-*b*]indol-3-ones **83**, including the parent compound **83a** (R^2 = H), with several mono- and disubstituted alkynes. The product distributions and, hence, the regioselectivities were sensitive to steric and electronic effects. For example, the results from the cycloadditions of **83a** fall into two groups (Scheme 18). First, reactions with terminal alkynes (entries 1–5), with the exception of methyl propynoate, gave mainly the 1,3-disubstituted carbazoles **98g–k**. These isomers were the only products of the reactions with phenylacetylene, 1-heptyne, and *tert*-butylacetylene. Second, when the hydrogen atom of the terminal acetylene was replaced by an alkyl, phenyl, or acyl group (entries 6–12), the regioselectivity was changed as a consequence of the controlling steric effects. The isomers **99l–r** are the main products. In these cases, the frontier orbital term is overcompensated by simple steric effects.

We have shown that **83a,b** also react with heterodienophiles. For example, the strongly polarized diethyl mesoxalate reacts under charge control[35] and hence with high regioselectivity to give the new pyranoindoles IV. These compounds are very unstable and decompose via cycloreversion to the more stable 2,3-difunctionalized indoles **102a,b**, respectively (Scheme 19).

The indolopyridones **103**, described for the first time in ref 28, represent indolo-2,3-quinodimethane analogues that are isoelectronic with **83**. The cycloaddition reactivity of these compounds with *N*-phenylmaleimide was tested (Scheme 20).[28] These and further investigations in our laboratory[35] showed that **103** exhibits a

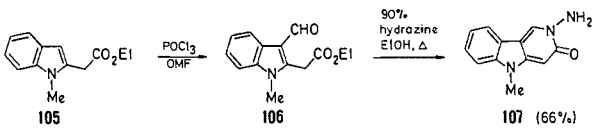
SCHEME 20



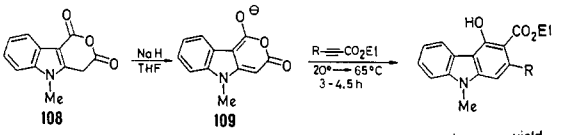
103	R
a	Me
b	Et

104	R	yield [%]
a	Me	88
b	Et	86

SCHEME 21



SCHEME 22



110	R	yield [%]
a	CO_2Et	45
b	H	21

lower enophile reactivity as compared with **83**. Cycloaddition reactions occur readily when the pure reactants are melted together. In this case, the Diels–Alder reaction stops at the stage of the primary adduct **104** since the isocyanic acid that would be formed on extrusion of the bridge represents an extremely poor retro dienophile.

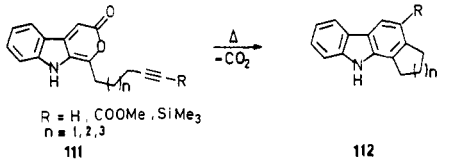
The synthesis of a 3-amino-substituted pyrido[4,3-*b*]indol-2-one was described recently,[40] but the potential Diels–Alder reactivity of the product has not yet been investigated. The selectively prepared 1,2-disubstituted indole **105** was subjected to a Vilsmeier formylation, and the resultant indole-3-carbaldehyde **106** was reacted with hydrazine to give the pyrido[4,3-*b*]indol-2-one **107** in 66% yield (Scheme 21).

Anionic pyranoindolones are also capable of undergoing [4 + 2]-cycloaddition/cycloreversion ($-CO_2$). Thus, deprotonation of 3-carboxy-1-methylindole-2-acetic anhydride (**108**) gives rise to the anionic cyclic indolo-2,3-quinodimethane **109**, which undergoes cyclization with diethyl acetylenedicarboxylate and ethyl propynoate to furnish the new 4-hydroxycarbazoles **110a,b** after extrusion of CO_2 (Scheme 22).[41] The regiochemistry obtained in the reaction with ethyl propynoate is without doubt the result of a charge-controlled orientation[6b] of the two reaction partners in the transition state.

V. Conclusions

The results of the numerous synthetic examples cited in the present review have demonstrated that in situ generation of indolo-2,3-quinodimethanes and, especially, the preparative use of stable cyclic analogues represent the method of choice for the highly regio- and stereoselective preparation of selectively functionalized [*b*]-anelated indoles, indole alkaloids, and carbazoles. With the use of further reactant combinations in the diene–dienophile system—including heterodienophiles—the syntheses of other anelated heterocycles of the indole series can be expected in the future. These

SCHEME 23



compounds should also be of interest from medicinal chemical points of view.

VI. Addendum

In a recent paper, the first intramolecular Diels–Alder reactions of pyrano[3,4-*b*]indol-3-ones were described.[42] The new 1-alkynylpyrano[3,4-*b*]indol-3-ones **111** were directly transformed under mild conditions and in good yields to the [*a*]-anelated carbazoles **112** (Scheme 23).

Recently, the first syntheses of the carbazole alkaloids carbazomycin A and B via the Diels–Alder reaction of 1-methylpyrano[3,4-*b*]indol-3-one with ethyl 3-(trimethylsilyl)propynoate were described.[43] In the same manner, the marine alkaloid hyellazole was prepared.[43]

VII. Acknowledgment

A part of the authors' work cited in this review was financially supported by the Deutsche Forschungsgemeinschaft, Bonn, FRG.

VIII. References

(1) Oppolzer, W. *Synthesis* **1978**, 793. Klundt, I. *Chem. Rev.* **1980**, *80*, 471. Charlton, J. L.; Alauddin, M. M. *Tetrahedron* **1987**, *43*, 2873. Funk, R. L.; Vollhardt, K. P. C. *Chem. Soc. Rev.* **1980**, *9*, 41.
(2) Rodrigo, R. *Tetrahedron* **1988**, *44*, 2093 and references cited therein.
(3) (a) 2*H*-Isoindoles as heterocyclic dienes: Kreher, R. P.; Use, G. *Chem. Ber.* **1988**, *121*, 927 and references cited therein. Kreher, R. P.; Hildebrand, T. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1262. (b) For other heteroaromatic *o*-quinodimethanes, see: Kaneko, C.; Naito, T. *Heterocycles* **1980**, *19*, 2183. Trahanovsky, W. S.; Cassady, T. J.; Woods, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 6691. Kaneko, C.; Naito, T. *Tetrahedron Lett.* **1981**, *22*, 2671 and references cited therein. Jullien, J.; Pechine, J.; Perez, F.; Piade, J. *Tetrahedron Lett.* **1980**, *21*, 611; **1979**, 3079. Vollhardt, K. P. C. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 411. Thummel, R. P.; Kohli, D. K. *Tetrahedron Lett.* **1979**, 143; *J. Org. Chem.* **1978**, *43*, 4882. Reimann, J. M.; Trahanovsky, W. S. *Tetrahedron Lett.* **1977**, 1867. Chow, D.; Khan, A. N.; Paddon-Row, M. *Aust. J. Chem.* **1975**, *28*, 1741. Paquette, L.; Kakihara, T. *J. Am. Chem. Soc.* **1971**, *93*, 174. Klemm, L.; Johnson, W. O.; White, D. V. *J. Heterocycl. Chem.* **1970**, *7*, 463. Huffman, K. R.; Loy, M.; Ullman, E. F. *J. Am. Chem. Soc.* **1965**, *87*, 5417. Scaiano, J. C.; Wintgens, V.; Bedell, A.; Berson, J. A. *J. Am. Chem. Soc.* **1988**, *110*, 4050. Chiba, T.; Kenny, P. W.; Miller, L. *J. Org. Chem.* **1987**, *52*, 4327. Gleiter, R.; Eckert-Maksić, M.; Konar, A. *Chem. Ber.* **1987**, *120*, 1917. Generation and reactions of 2,3-dimethylene-2,3-dihydrothiophene and benzothiophene analogues: Chauhan, P. M. S.; Jenkins, G.; Walkers, S. M.; Storr, R. C. *Tetrahedron Lett.* **1988**, *29*, 117. Dyker, D.; Kreher, R. P. *Chem. Ber.* **1988**, *121*, 1203.
(4) Jacob, D.; Niedermann, H. P.; Meier, H. *Tetrahedron Lett.* **1986**, *27*, 5703. Meier, H.; Eckes, H. L.; Niedermann, H. P.; Kolshorn, H. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1046.
(5) Pindur, U.; Akgün, E. *Chem.-Ztg.* **1984**, *108*, 371. Pindur, U.; Pfeuffer, L. *Chem.-Ztg.* **1986**, *110*, 95. Pindur, U.; Pfeuffer, L.; Flo, C. *Chem.-Ztg.* **1986**, *110*, 307. Saxton, J. E. *Indoles, Part Four, The Monoterpenoid Indole Alkaloids*; Wiley: New York, 1983 and references cited therein. Brossi, A. *The Alkaloids*; Academic Press: New York, 1985; Vol 26.
(6) (a) Dewar, M. J. S.; Thiel, W. *J. Am. Chem. Soc.* **1977**, *99*, 4899, 4907. (b) Fleming, I. *Frontier Orbitals and Chemical Reactions*; Wiley: New York, 1976.
(7) Marinelli, E. R. *Tetrahedron Lett.* **1982**, *23*, 2745.
(8) Saroja, B.; Srinivasan, P. C. *Tetrahedron Lett.* **1984**, *25*, 5429.
(9) Kurihara, T.; Hanakawa, M.; Wakita, T.; Harusawa, S. *Heterocycles* **1985**, *23*, 2221. Kurihara, T.; Hanakawa, M.; Harusawa, S.; Yoneda, R. *Chem. Pharm. Bull.* **1986**, *34*, 4545.
(10) Bergman, J.; Carlsson, R. *Tetrahedron Lett.* **1977**, 4663.
(11) Kano, S.; Sugino, E.; Shibuya, S.; Hibino, S. *J. Org. Chem.* **1981**, *46*, 2979.
(12) Gallagher, T.; Magnus, P. *J. Am. Chem. Soc.* **1983**, *105*, 2086, 4739.
(13) Magnus, P.; Gallagher, T. *Tetrahedron* **1981**, *37*, 3889.
(14) Magnus, P.; Gallagher, T.; Brown, P.; Pappalardo, P. *Acc. Chem. Res.* **1984**, *17*, 35 and references cited therein.
(15) Magnus, P.; Gallagher, T.; Brown, P.; Huffman, J. C. *J. Am. Chem. Soc.* **1984**, *106*, 2105.
(16) Cardwell, K.; Hewitt, B.; Ladlow, M.; Magnus, P. *J. Am. Chem. Soc.* **1988**, *110*, 2242 and references cited therein.
(17) Gallagher, T.; Magnus, P.; Huffman, J. C. *J. Am. Chem. Soc.* **1982**, *104*, 1140.
(18) Herslöf, M.; Martin, A. R. *Tetrahedron Lett.* **1987**, *28*, 3423.
(19) Welch, W. M. *J. Org. Chem.* **1976**, *41*, 2031.
(20) Sha, C.-K.; Chuang, K.-S.; Young, J. J. *J. Chem. Soc., Chem. Commun.* **1984**, 1552.
(21) Sha, C.-K.; Chuang, K.-S.; Wey, C.-J. *J. Chem. Soc., Perkin Trans. 1* **1987**, 977.
(22) Kreher, R. P.; Dyker, G. *Z. Naturforsch.* **1987**, *42b*, 473.
(23) Saulnier, M. G.; Gribble, G. W. *Tetrahedron Lett.* **1983**, *24*, 5435.
(24) Gribble, G. W.; Saulnier, M. G.; Sibi, M. P.; Obaza-Nutaitis, J. A. *J. Org. Chem.* **1984**, *49*, 4518.
(25) Kansal, V. K.; Potier, P. *Tetrahedron* **1986**, *42*, 2389. Gribble, G. W.; Saulnier, M. G. *Heterocycles* **1985**, *23*, 1277. Pindur, U. *Pharmazie Unserer Zeit* **1987**, *16*, 47.
(26) Gribble, G. W.; Saulnier, M. G. *J. Chem. Soc., Chem. Commun.* **1984**, 168.
(27) Shafiee, A.; Sattari, S. *J. Heterocycl. Chem.* **1982**, *19*, 227.
(28) Plieninger, H.; Müller, W.; Weinerth, K. *Chem. Ber.* **1964**, *97*, 667.
(29) Moody, C. J. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2505. Moody, C. J. *J. Chem. Soc., Chem. Commun.* **1984**, 925.
(30) Narasimhan, N. S.; Gokhale, S. M. *J. Chem. Soc., Chem. Commun.* **1985**, 85.
(31) May, C.; Moody, C. J. *J. Chem. Soc., Chem. Commun.* **1984**, 926.
(32) May, C.; Moody, C. J. *J. Chem. Soc., Perkin Trans. 1* **1988**, 247.
(33) Pindur, U.; Abdoust-Houshang, E. *Chimia* **1988**, *42*, 180.
(34) Pindur, U.; Abdoust-Houshang, E. *Liebigs Ann. Chem.* **1988**, 803.
(35) Pindur, U.; Abdoust-Houshang, E. *Liebigs Ann. Chem.* **1989**, 227. Pindur, U.; Abdoust-Houshang, E. *Heterocycles*, in press.
(36) MNDO calculations: program packet MOPAC; Stewart, J. P. *QCPE Bull.* **1983**, *3*, 455; see ref 6a.
(37) Retro-Diels–Alder strategy in natural product synthesis: Lasne, M.-C.; Ripoll, J.-L. *Synthesis* **1985**, 121. Ripoll, J.-L.; Rouessac, A.; Rouessac, F. *Tetrahedron* **1978**, *34*, 19. Ichihara, A. *Synthesis* **1987**, 207.
(38) Birch, A. J.; Jackson, A. H.; Shannon, P. V. R. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2185.
(39) Moody, C. J.; Shah, P. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1407.
(40) Karrick, G. L.; Peet, N. P. *J. Heterocycl. Chem.* **1986**, *23*, 1055.
(41) Tamura, Y.; Mohri, S.; Maeda, H.; Tsugoshi, T.; Sasho, M.; Kita, Y. *Tetrahedron Lett.* **1984**, *25*, 309.
(42) Moody, C. J.; Shah, P.; Knowles, P. *Tetrahedron Lett.* **1988**, *29*, 2693.
(43) Moody, C. J.; Shah, P. *J. Chem. Soc., Perkin Trans. 1* **1989**, 376.