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INVERSE-ELECTRON-DEMAND DIELS-ALDER REACTIONS OF CONDENSED PYRIDAZINES, PART 2.[1,2] SYNTHESIS OF ISOQUINOLINE DERIVATIVES FROM PYRIDO[3,4-*d*]PYRIDAZINES.

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Abstract: Employment of pyrido[3,4-*d*]pyridazine derivatives **1**, **2**, **3** as aza-dienes in inverse-electron-demand Diels-Alder reactions with 1-pyrrolidino-1-cyclopentene or its six-membered homologue, respectively, was found to provide an easy access to the isoquinolines **5**, **7**, **9**, **11**, **13**, **15** after aromatisation of intermediate mixtures of regioisomeric dihydroisoquinoline derivatives.

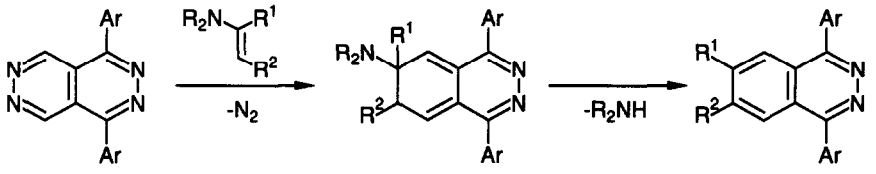
The utilisation of [4+2] cycloaddition reactions of electron-poor dienes with electron-rich dienophiles for the synthesis of carbocyclic as well as heterocyclic systems has become a well-established methodology over the past years. Since the publication of the first examples[3,4] of such an inverse-electron-demand variant of the Diels-Alder reaction (which has been predicted[5] already in 1949), this reaction type has received more and more interest.[6] The development of the Woodward-Hoffmann rules[7] and the FMO (frontier molecular orbital) theory[8] provided the theoretical basis for the understanding of a rapidly increasing number of experimental results.

In particular, six-membered N-heteroaromatic systems are well-suited to participate as dienes in inverse-electron-demand ($LUMO_{diene}$-controlled) Diels-Alder reactions, due to their π-electron deficient properties. As follows from the corresponding LUMO energies, tetrazines - in general - are more reactive than triazines, the latter being better dienes than diazines and - finally - pyridine.[6] Accordingly, the presence of electron-withdrawing substituents in such heteroaromatic (aza-)dienes significantly enhances their reactivity towards

electron-rich dienophiles like enamines, alkynes, or ketene acetals. In a similar way, the annelation of a second six-membered N-heteroaromatic ring to a π-deficient system usually leads to a decrease in its LUMO energy and thus can be anticipated to favour inverse Diels-Alder reactions.

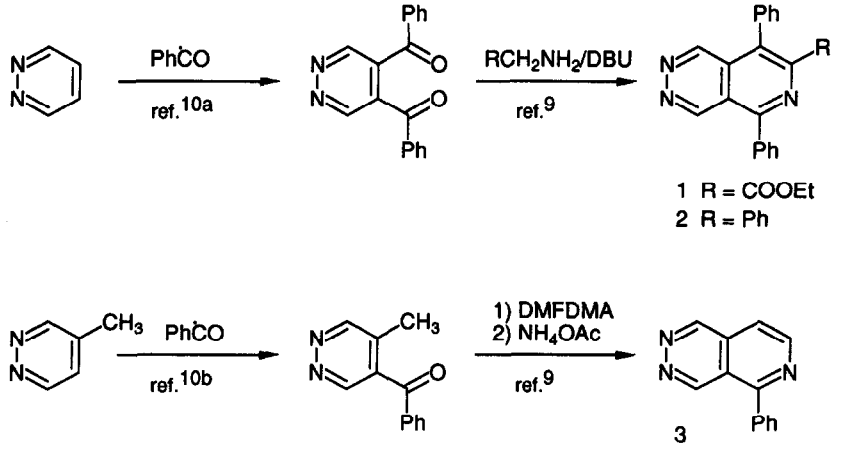
In continuation of previous investigations of the Diels-Alder cycloaddition behaviour of pyridazino[4,5-*d*]pyridazines[1] (see Scheme 1), the present paper describes the utilisation of another type of condensed pyridazines, namely pyrido[3,4-*d*]pyridazines, as activated aza-dienes, giving rise to the synthesis of a series of hitherto unknown isoquinoline derivatives.

Scheme 1.



As starting materials for the present investigations, the 5,7,8-trisubstituted pyrido[3,4-*d*]pyridazines **1,2** and the 5-phenyl-diazaisoquinoline **3** were chosen. The synthesis of these compounds, which has been described earlier,[9] is based on radicalic benzoylation of pyridazine or 4-methylpyridazine, respectively, as the first reaction step.[10]

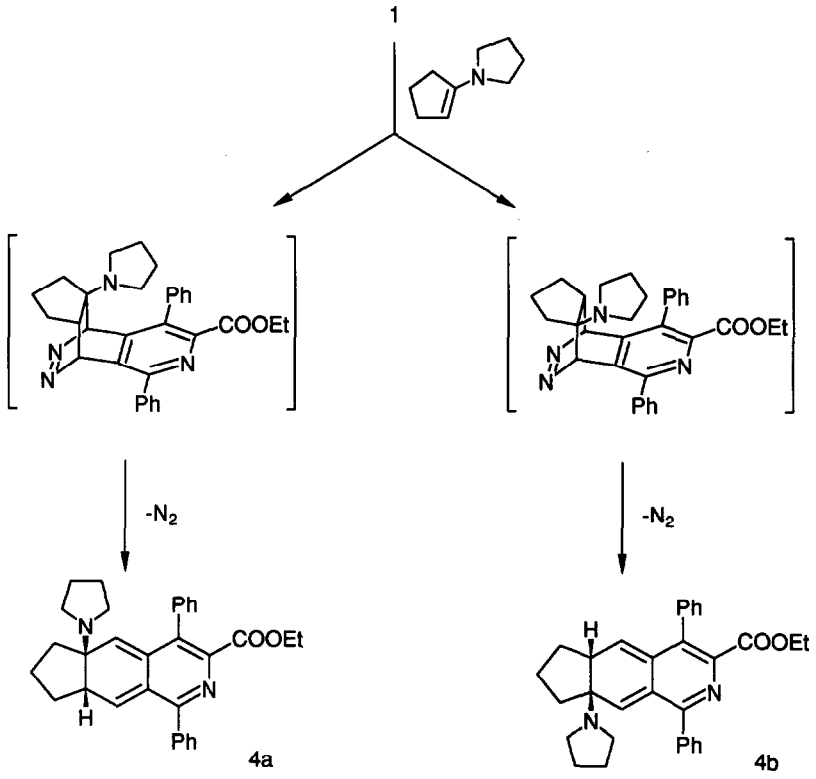
Scheme 2.



Although the LUMO energies (which were obtained by semiempirical AM1[11] calculations) of the triazanaphthalenes **1** (-1.46 eV) and **2,3** (each -1.23 eV) are somewhat higher than that of the reactive aza-diene 1,4-diphenylpyridazino[4,5-*d*]pyridazine (-1.60 eV), these pyrido[3,4-*d*]pyridazines can be expected to undergo [4+2] cycloaddition reactions with electron-rich dienophiles like 1-pyrrolidino-1-cyclopentene or 1-pyrrol-

idino-1-cyclohexene under comparably mild conditions. Indeed, when the ester **1** was refluxed with a fourfold excess of the cyclopentanone-derived enamine in dioxane solution, the starting material was completely consumed within one hour (reaction monitoring by TLC). In contrast to the special case of the previously studied, symmetrically disubstituted tetraaza-naphthalenes (Scheme 1), employment of a pyrido[3,4-*d*]pyridazine azadiene for cycloaddition with an enamine can be anticipated to give rise to the formation of two isomeric reaction products (after spontaneous loss of nitrogen from an initially formed, highly strained cycloadduct; cf. Scheme 3[12]). ^{1}H-NMR spectra of the crude reaction mixture proved this to be the case. Obviously, two isomeric (cyclopentane-fused) dihydroisoquinolines (compounds **4a,b**) are formed in this transformation, resulting from attack of the dienophile at the sterically less hindered ring of the bicyclic system.[13]

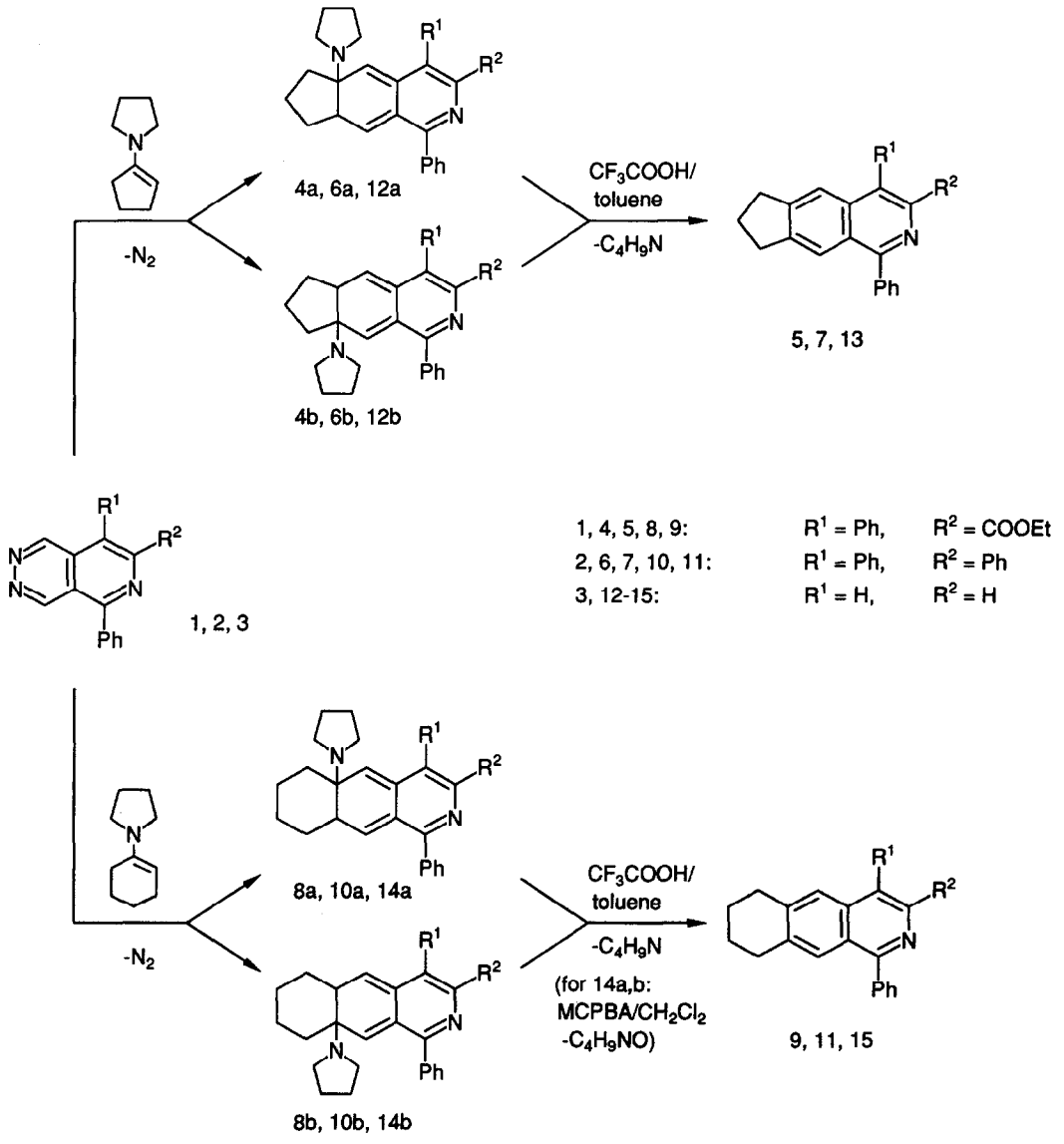
Scheme 3.



Whereas a product ratio of 2.5:1 could be determined by ^{1}H-NMR (relative intensities of the separated signals of the olefinic protons at ca. 6 ppm), spectral information did not permit a definitive conclusion, which isomer (**4a** or **4b**) is the predominant one.[14] Moreover, attempted separation of compounds **4a,b** failed, owing to their very similar chromatographic behaviour. However, it was found that the mixture **4a/4b** can be easily transformed into a single final product (compound **5**) by acid-catalyzed elimination of pyrrolidine, a method (refluxing in toluene/trifluoroacetic acid) which had been previously employed for the aromatisation of structurally closely related dihydrophthalazine derivatives.[1]

When the triphenyl-substituted pyrido[3,4-*d*]pyridazine **2** was treated with 1-pyrrolidino-1-cyclopentene in an analogous way as described for the ester **1**, the required reaction time was significantly longer (8 hours compared to 1 hour for **1**, see above). Obviously, this reflects the higher LUMO energy of compound **2**. Also in this case, a mixture of two isomeric products (**6a** and **6b**) was formed. Here, a ratio of 15:1 (**a**:**b** or **b**:**a**) follows from a ^{1}H-NMR spectrum of the crude reaction mixture. Again, the dihydro products thus obtained could be aromatised under acidic conditions to give a single (aromatic) isoquinoline derivative (compound **7**) in high yield.

Scheme 4.



As observed earlier,[1] the six-membered enamine 1-pyrrolidino-1-cyclohexene was found to be a significantly less reactive dienophile than the cyclopentanone-derived analog. On treatment of **1** as well as of **2** with this reagent, the periods required for complete consumption of the azadiene components were about one order of magnitude longer (8 hours and 92 hours) than those for the transformations **1** → **4** and **2** → **6**. The product ratios - 3:1 for compounds **8**, 14:1 for compounds **10** - are similar to those observed for the reactions with the five-membered enamine. Interestingly, with the cyclohexane-fused dihydroisoquinolines **8a,b** and **10a,b** also the acid-catalysed aromatisation reactions were found to proceed considerably slower (requiring 24 hours of refluxing) than in the case of compounds **4a,b** and **6a,b**. This has to be ascribed to conformational reasons, as will be discussed later. Nevertheless, the condensed isoquinolines **9** and **11** can be obtained by this procedure in good overall yields.

Expectedly, reaction of the monosubstituted pyrido[3,4-*d*]pyridazine **3** with the same cyclic enamines as described above again yielded mixtures of isomeric dihydroisoquinoline derivatives. However, here it was possible to isolate the major component of the **12a/12b** mixture as well as both **14a** and **14b** by means of medium-pressure liquid chromatography. Moreover, NOE difference spectroscopy provided an unambiguous structural assignment for these compounds (see Figure 1): in the case of **12a**, saturation of the pyridine proton in position 4 led to a significant Nuclear Overhauser Enhancement for the signal of the olefinic proton at lower field (6.15 ppm; H-5, adjacent to the pyrrolidine nitrogen atom) and not for the corresponding signal at higher field (4.42 ppm; H-9, adjacent to the angular proton at C-8a; $J_{8a\text{-}9}$ = 11.4 Hz). Analogously, the structure of compound **14a** follows from an observed NOE between H-4 and the *downfield* olefinic proton signal (at 6.17 ppm), whereas the corresponding experiment for **14b** shows an NOE for the *upfield* signal (3.68 ppm). Based on these assignments, the cycloaddition product ratios could be determined as **12a**:**12b** = 5:1 and **14a**:**14b** = 3:1.

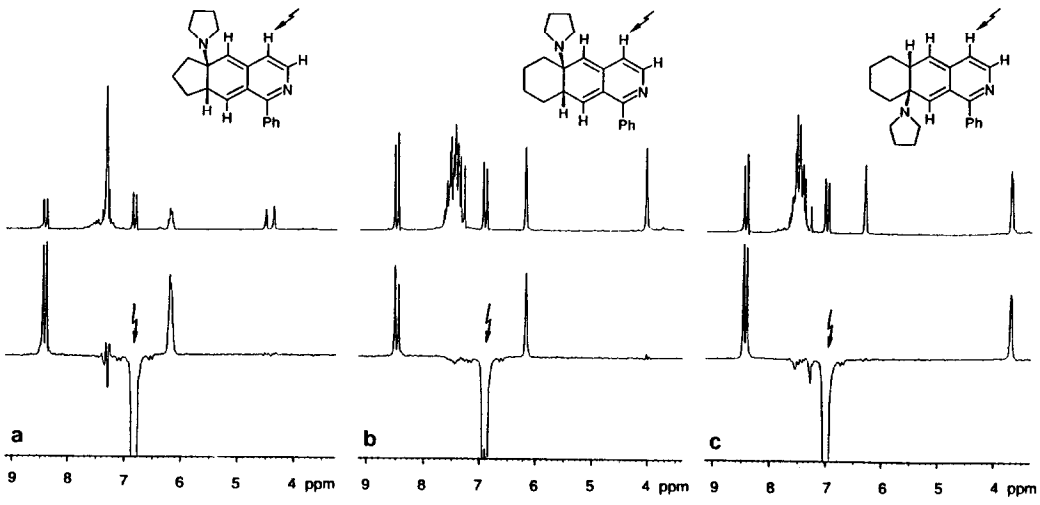


Figure 1. Downfield region of the 80 MHz ^{1}H NMR spectra (upper traces) and NOE difference spectra (lower traces) of compounds **12a** (a), **14a** (b), and **14b** (c); $CDCl_3$, 25°C.

Similar to the transformations **4a/4b** → **5** and **6a/6b** → **7**, refluxing of the mixture **12a/12b** in toluene/trifluoroacetic acid smoothly led to elimination of pyrrolidine from the dihydroisoquinolines within 2 hours, affording the cyclopent[*g*]isoquinoline **13** in 83% overall yield. In contrast, in the case of the analogous step **14a/14b** → **15** even prolonged reaction times (> 7d) did not give more than a 10% yield of **15** under comparable conditions. Also attempted thermally-induced pyrrolidine elimination under neutral conditions (in analogy to the successful aromatisation of acid-sensitive condensed dihydrophthalazine derivatives[1]) gave only poor yields. As the torsion angle of the leaving groups plays a key role in the rate of an E_2 elimination process, the pyrrolidine nitrogen atom and the angular proton involved in this reaction must be particularly poorly aligned in the case of compounds **14**. A similar observation has been described recently by Chenard et al.[15] for an analogous cyclohexane-annelated dihydropyridine derivative (a 1-substituted 4a,5,6,7,8,8a-hexahydro-8a-pyrrolidinylisoquinoline), where an unfavourable torsion angle of 52.28° (determined by X-ray crystallography) between the leaving groups had been found to be responsible for low elimination yields.

To gain more insight into this problem, the energy-minimised conformations for compounds **12a** and **14a** were calculated with a force-field program,[16] assuming *cis* annelation[17] of the cyclopentane or cyclohexane ring, respectively, to the dihydroisoquinoline system. The results show a torsion angle of 29.4° for the leaving groups in compound **12a** and, indeed, a considerably less favourable torsion angle of 49.0° in the case of compound **14a** (cf. Figure 2). The calculated structures are in good agreement with the ^{1}H-NMR spectra of **12a** and **14a**. For compound **12a**, the doublet of H-9 (at 4.42 ppm) shows a coupling constant of 11.4 Hz for the interaction with H-8a, thus reflecting the (calculated) torsion angle of 38.8° between these two protons (also the signal of the olefinic proton at C-5 exhibits slight splitting, obviously due to long-range couplings). In contrast, in the spectrum of compound **14a**, the corresponding signal (H-10) appears as a singlet, which strongly supports the calculated torsion angle of 89.1° between this proton and the adjacent angular proton at C-9a (cf. Figures 1a, 1b, upper traces).

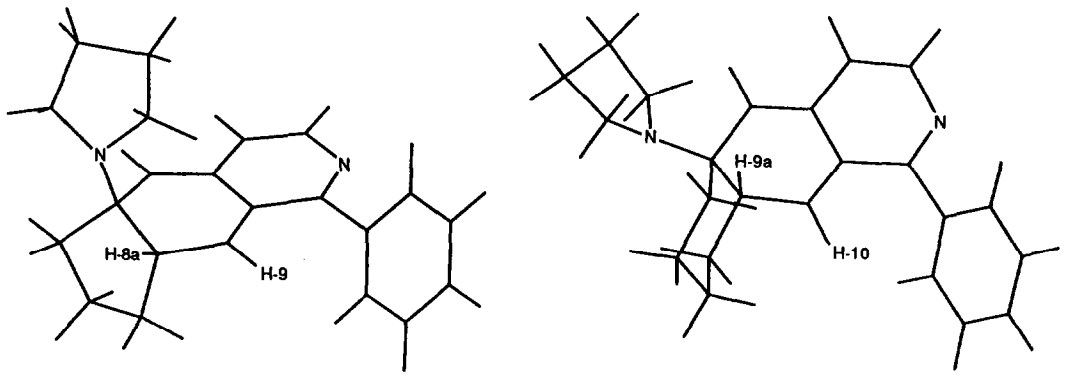


Figure 2. Energy-minimised[16] structures of compounds **12a** (left) and **14a** (right).

Finally, the problem of sluggish pyrrolidine elimination from compounds **14a,b** could be overcome - in analogy to Chenard's procedure[15] - by selective oxidation of the pyrrolidine nitrogen atom with *m*-chloro-

perbenzoic acid in dichloromethane solution at room temperature. Under these conditions, the N-oxide thus formed spontaneously undergoes a (cyclic) elimination process with loss of N-hydroxypyrrolidine to afford the cyclohexane-fused isoquinoline **15** in 73% isolated yield (referred to **3**).

As demonstrated, the reaction of pyrido[3,4-*d*]pyridazines with enamines provides an easy access to isoquinoline derivatives with a particular substitution pattern and represents another example for the successful employment of condensed pyridazines as aza-dienes in inverse-electron-demand Diels-Alder reactions.[18] At present, the utilisation of appropriately substituted (mono- and bicyclic) pyridazines in *intra*molecular [4+2] cycloaddition reactions is being studied.

EXPERIMENTAL

Melting points (uncorrected) were determined on a Kofler hot-stage microscope. ^{1}H-NMR spectra were recorded on a Bruker AC 80 (80 MHz) spectrometer (TMS as internal reference, δ-values in ppm), high-resolution mass spectra were obtained on a Finnigan MAT 8230 (equipped with a data system SS300). Column chromatography was done on Merck Kieselgel 60, 0.063-0.200 mm, medium-pressure liquid chromatography (MPLC) was carried out on Merck LiChroprep Si 60, 0.040-0.063 mm (detection at 280 nm). Microanalyses[19] were performed at the Institute of Physical Chemistry (Microanalytical Laboratory), University of Vienna.

Cycloaddition Reaction of Ethyl 5,8-Diphenylpyrido[3,4-*d*]pyridazine-7-carboxylate (**1**) with 1-Pyrrolidino-1-cyclopentene.

A solution of the ester **1**[9] (178 mg; 0.5 mmol) and 1-pyrrolidino-1-cyclopentene[20] (274 mg; 2 mmol) in dry 1,4-dioxane (5 ml) was refluxed for 1 h under an atmosphere of argon. The volatile components were distilled off under reduced pressure, polymeric material was removed by short-column chromatography (eluting with dichloromethane/ethyl acetate, 1:1). The oily **4a/4b** mixture thus obtained was dissolved in toluene (10 ml). Trifluoroacetic acid (0.5 ml) was added, and the mixture was refluxed for 2 h. The oily residue left after evaporation of the solvent was partitioned between a saturated aqueous solution of sodium hydrogencarbonate and dichloromethane. The organic layer was washed with water, dried, and evaporated. Purification by short-column chromatography (eluting with dichloromethane/ethyl acetate, 3:1) afforded ethyl 7,8-dihydro-1,4-diphenyl-6*H*-cyclopent[*g*]isoquinoline-3-carboxylate (**5**) (173 mg; 87%) as colourless crystals, mp 182-183°C (ethanol). - ^{1}H-NMR ($CDCl_3$) δ 7.93 (s, 1 H, H-5 or H-9), 7.85-7.30 (m, 11 H, H-9 or H-5, C_6H_5), 4.10 (q, J = 7.1 Hz, 2 H, $OC\underline{H}_2CH_3$), 3.15-2.85 (m, 4 H, $C\underline{H}_2CH_2C\underline{H}_2$), 2.35-1.85 (m, 2 H, $CH_2C\underline{H}_2CH_2$), 0.97 (t, J = 7.1 Hz, 3 H, $OCH_2C\underline{H}_3$). - HRMS Calcd. for $C_{27}H_{23}NO_2$: m/z 393.1729. Found: 393.1725. - Anal. Calcd. for $C_{27}H_{23}NO_2 \cdot 0.2\ H_2O$: C, 81.67; H, 5.94; N, 3.53. Found: C, 81.67; H, 6.18; N, 3.46.

Cycloaddition Reaction of 5,7,8-Triphenylpyrido[3,4-*d*]pyridazine (2) with 1-Pyrrolidino-1-cyclopentene.

A solution of compound[9] **2** (180 mg; 0.5 mmol) and 1-pyrrolidino-1-cyclopentene[20] (274 mg; 2 mmol) in dry 1,4-dioxane (5 ml) was refluxed for 8 h under an atmosphere of argon. The volatile components were distilled off under reduced pressure, polymeric material was removed by short-column chromatography (eluting with dichloromethane/ethyl acetate, 1:1). The oily **6a/6b** mixture thus obtained was dissolved in toluene (10 ml). Trifluoroacetic acid (0.5 ml) was added, and the mixture was refluxed for 2 h. The oily residue left after evaporation of the solvent was partitioned between a saturated aqueous solution of sodium hydrogencarbonate and dichloromethane. The organic layer was washed with water, dried, and evaporated. Purification by short-column chromatography (eluting with dichloromethane/ethyl acetate, 4:1) afforded 7,8-dihydro-1,3,4-triphenyl-6*H*-cyclopent[*g*]isoquinoline (**7**) (184 mg; 91%) as colourless crystals, mp 214-215°C (ethanol). - ^{1}H-NMR ($CDCl_3$) δ 7.95 (s, 1 H, H-5 or H-9), 7.90-7.05 (m, 16 H, H-9 or H-5, C_6H_5), 3.10-2.85 (m, 4 H, $CH_2CH_2CH_2$), 2.35-1.90 (m, 2 H, $CH_2CH_2CH_2$). - HRMS Calcd. for $C_{30}H_{23}N$: m/z 397.1830. Found: 397.1812. - Anal. Calcd. for $C_{30}H_{23}N \cdot 0.4\ H_2O$: C, 89.03; H, 5.93; N, 3.46. Found: C, 89.15; H, 6.01; N, 3.41.

Cycloaddition Reaction of Ethyl 5,8-Diphenylpyrido[3,4-*d*]pyridazine-7-carboxylate (1) with 1-Pyrrolidino-1-cyclohexene.

A solution of the ester **1**[9] (178 mg; 0.5 mmol) and 1-pyrrolidino-1-cyclohexene[20] (302 mg; 2 mmol) in dry 1,4-dioxane (5 ml) was refluxed for 8 h under an atmosphere of argon. The volatile components were distilled off under reduced pressure, polymeric material was removed by short-column chromatography (eluting with dichloromethane/ethyl acetate, 1:2). The oily **8a/8b** mixture thus obtained was dissolved in toluene (10 ml). Trifluoroacetic acid (0.5 ml) was added, and the mixture was refluxed for 24 h. The oily residue left after evaporation of the solvent was partitioned between a saturated aqueous solution of sodium hydrogencarbonate and dichloromethane. The organic layer was washed with water, dried, and evaporated. Purification by short-column chromatography (eluting with dichloromethane/ethyl acetate, 3:1) afforded ethyl 6,7,8,9-tetrahydro-1,4-diphenylbenz[*g*]isoquinoline-3-carboxylate (**9**) (163 mg; 79%) as colourless crystals, mp 181-182°C (ethanol). - ^{1}H-NMR ($CDCl_3$) δ 7.83 (s, 1 H, H-5 or H-10), 7.80-7.30 (m, 11 H, H-10 or H-5, C_6H_5), 4.10 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 3.05-2.70 (m, 4 H, $CH_2CH_2CH_2CH_2$), 1.95-1.70 (m, 4 H, $CH_2CH_2CH_2CH_2$), 0.98 (t, J = 7.1 Hz, 3 H, OCH_2CH_3). - HRMS Calcd. for $C_{28}H_{25}NO_2$: m/z 407.1885. Found: 407.1875. - Anal. Calcd. for $C_{28}H_{25}NO_2 \cdot 0.3\ H_2O$: C, 81.45; H, 6.25; N, 3.39. Found: C, 81.28; H, 6.31; N, 3.36.

Cycloaddition Reaction of 5,7,8-Triphenylpyrido[3,4-*d*]pyridazine (2) with 1-Pyrrolidino-1-cyclohexene.

A solution of compound[9] **2** (180 mg; 0.5 mmol) and 1-pyrrolidino-1-cyclohexene[20] (302 mg; 2 mmol) in dry 1,4-dioxane (5 ml) was refluxed for 92 h under an atmosphere of argon. The volatile components were distilled off under reduced pressure, polymeric material was removed by short-column chromatography (eluting with dichloromethane/ethyl acetate, 1:2). The semi-solid **10a/10b** mixture thus obtained was dissolved in toluene (10 ml). Trifluoroacetic acid (0.5 ml) was added, and the mixture was refluxed for 24 h. The solid residue left after evaporation of the solvent was partitioned between a saturated aqueous solution of sodium hydrogencarbonate and dichloromethane. The organic layer was washed with water, dried, and

evaporated. Purification by short-column chromatography (eluting with dichloromethane/ethyl acetate, 3:1) afforded 6,7,8,9-tetrahydro-1,3,4-triphenylbenz[*g*]isoquinoline (**11**) (160 mg; 76%) as colourless crystals, mp 222-224°C (ethanol). - ^{1}H-NMR ($CDCl_3$) δ 7.86 (s, 1 H, H-5 or H-10), 7.85-7.05 (m, 16 H, H-10 or H-5, C_6H_5), 3.05-2.70 (m, 4 H, $C\underline{H}_2CH_2CH_2C\underline{H}_2$), 2.00-1.70 (m, 4 H, $CH_2C\underline{H}_2C\underline{H}_2CH_2$). - HRMS Calcd. for $C_{31}H_{25}N$: m/z 411.1986. Found: 411.1976. - Anal. Calcd. for $C_{31}H_{25}N \cdot 0.5\ H_2O$: C, 88.54; H, 6.23; N, 3.33. Found: C, 88.56; H, 6.30; N, 3.30.

Cycloaddition Reaction of 5-Phenylpyrido[3,4-*d*]pyridazine (**3**) with 1-Pyrrolidino-1-cyclopentene.

A solution of compound[9] **3** (207 mg; 1 mmol) and 1-pyrrolidino-1-cyclopentene[20] (548 mg; 4 mmol) in dry 1,4-dioxane (10 ml) was refluxed for 7 h under an atmosphere of argon. The volatile components were distilled off under reduced pressure, polymeric material was removed by short-column chromatography (eluting with dichloromethane/ethyl acetate, 4:1). The oily mixture **12a/12b** thus obtained was used for the following elimination step (see below) without further purification.

Isolation of compound **12a**: the mixture **12a/12b** was subjected to MPLC (eluting with dichloromethane/ethyl acetate, 4:1). By careful fraction cutting, a sample of chromatographically pure 5a,7,8,8a-tetrahydro-1-phenyl-5a-pyrrolidino-6*H*-cyclopent[*g*]isoquinoline (**12a**) was obtained as an almost colourless oil which slowly became dark. ^{1}H-NMR ($CDCl_3$) δ 8.40 (d, J = 4.9 Hz, 1 H, H-3), 7.65-7.20 (m, 5 H, C_6H_5), 6.80 (d, J = 4.9 Hz, 1 H, H-4), 6.20-6.10 (m, unresolved, 1 H, H-5; shows NOE on irradiation of d at 6.80 ppm), 4.42 (d, J = 11.4 Hz, 1 H, H-9), 3.10-1.00 (m, 15 H, H-8a, NCH_2C, CCH_2C).

7,8-Dihydro-1-phenyl-6*H*-cyclopent[*g*]isoquinoline (**13**).

The crude mixture of **12a/12b**, obtained as described above, was dissolved in toluene (20 ml). Trifluoroacetic acid (1 ml) was added, and the solution was refluxed for 2 h. The oily residue left after evaporation of the solvent was partitioned between a saturated aqueous solution of sodium hydrogencarbonate and dichloromethane. The organic layer was washed with water, dried, and evaporated. Purification by column chromatography (eluting with dichloromethane/ethyl acetate, 9:1) afforded compound **13** (205 mg; 83%) as a colourless oil which slowly crystallised, mp 101-103°C (diethyl ether/n-pentane). - ^{1}H-NMR ($CDCl_3$) δ 8.49 (d, J = 5.7 Hz, 1 H, H-3), 7.85 (s, 1 H, H-5 or H-9), 7.75-7.35 (m, 7 H, H-4, H-9 or H-5, C_6H_5), 3.15-2.85 (m, 4 H, $C\underline{H}_2CH_2C\underline{H}_2$), 2.30-1.90 (m, 2 H, $CH_2C\underline{H}_2CH_2$). - HRMS Calcd. for $C_{18}H_{15}N$: m/z 245.1204. Found: 245.1196. - Anal. Calcd. for $C_{18}H_{15}N \cdot 0.1\ H_2O$: C, 87.48; H, 6.20; N, 5.67. Found: C, 87.68; H, 6.31; N, 5.72.

Cycloaddition Reaction of 5-Phenylpyrido[3,4-*d*]pyridazine (**3**) with 1-Pyrrolidino-1-cyclohexene.

A solution of compound[9] **3** (207 mg; 1 mmol) and 1-pyrrolidino-1-cyclohexene[20] (604 mg; 4 mmol) in dry 1,4-dioxane (10 ml) was refluxed for 72 h under an atmosphere of argon. The volatile components were distilled off under reduced pressure, polymeric material was removed by short-column chromatography

(eluting with ethyl acetate/ethanol, 4:1). The oily mixture **14a/14b** thus obtained was used for the following elimination step (see below) without further purification.

Isolation of compounds **14a** and **14b**: the mixture was subjected to MPLC (eluting with ethyl acetate/ethanol, 92:8). After a fraction containing a minor amount of compound **15** (see below), the second fraction yielded - after evaporation - 5a,6,7,8,9,9a-hexahydro-1-phenyl-5a-pyrrolidinobenz[*g*]isoquinoline (**14a**) (202 mg; 61%) as an almost colourless oil which slowly became dark. ^{1}H-NMR ($CDCl_3$) δ 8.47 (d, J = 4.9 Hz, 1 H, H-3), 7.65-7.30 (m, 5 H, C_6H_5), 6.89 (d, J = 4.9 Hz, 1 H, H-4), 6.17 (s, 1 H, H-5; shows NOE on irradiation of d at 6.89 ppm), 4.02 (s, 1 H, H-10), 2.65-1.15 (m, 17 H, H-9a, NCH_2C, CCH_2C). Work-up of the third fraction afforded 5a,6,7,8,9,9a-hexahydro-1-phenyl-9a-pyrrolidinobenz[*g*]isoquinoline (**14b**) (66 mg; 20%) as an almost colourless oil which slowly became dark. ^{1}H-NMR ($CDCl_3$) δ 8.43 (d, J = 4.8 Hz, 1 H, H-3), 7.70-7.30 (m, 5 H, C_6H_5), 6.98 (d, J = 4.8 Hz, 1 H, H-4), 6.29 (s, 1 H, H-10), 3.68 (d, J = 1.6 Hz, 1 H, H-5; shows NOE on irradiation of d at 6.98 ppm), 2.65-1.10 (m, 17 H, H-5a, NCH_2C, CCH_2C).

6,7,8,9-Tetrahydro-1-phenylbenz[*g*]isoquinoline (**15**).

The crude mixture of **14a/14b**, obtained as described above, was dissolved in dichloromethane (20 ml). After addition of 50% *m*-chloroperbenzoic acid (345 mg; 1 mmol), the mixture was stirred at room temperature for 2 h. The solution was diluted with dichloromethane (30 ml), then it was washed with 0.5 *N* aqueous sodium hydroxide and subsequently with water and brine. The oily residue obtained after removal of the solvent was subjected to column chromatography (eluting with dichloromethane/ethyl acetate, 9:1) to give compound **15** (190 mg; 73%) as a colourless oil which slowly crystallised, mp 106-108°C (n-pentane). - ^{1}H-NMR ($CDCl_3$) δ 8.47 (d, J = 5.7 Hz, 1 H, H-3), 7.75 (s, 1 H, H-5 or H-10), 7.70-7.40 (m, 7 H, H-4, H-10 or H-5, C_6H_5), 3.10-2.70 (m, 4 H, $CH_2CH_2CH_2CH_2$), 2.00-1.65 (m, 4 H, $CH_2CH_2CH_2CH_2$). - HRMS Calcd. for $C_{19}H_{17}N$: m/z 259.1361. Found: 259.1360. - Anal. Calcd. for $C_{19}H_{17}N \cdot 0.1\ H_2O$: C, 87.39; H, 6.64; N, 5.36. Found C, 87.34; H, 6.87; N, 5.41.

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12. For clarity, the graphical representation of other possible endo/exo isomers and enantiomers was omitted in Scheme 3.

13. Although the LUMO p_z coefficients at the pyridine carbon atoms C-5 and C-8 are slightly higher than those at the pyridazine carbon atoms C-1 and C-4 (according to AM1 calculations), not even traces of reaction products resulting from cycloaddition across C-5/C-8 could be detected.

14. Not surprisingly, there is no significant difference in the LUMO p_z coefficients (C-1: 0.356, C-4: 0.348) and in the partial charges of the involved pyridazine carbon atoms. Thus, a simple estimation on the basis of these calculations (AM1) with respect to the preferred orientation of diene/dienophile is not possible.

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17. This assumption appears to be justified, taking into account the mechanism of a [4+2] cycloaddition reaction, whether it may follow a "pure" concerted pathway or (more probably) involves a transition state with some degree of charge separation.

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19. As observed earlier for structurally related phthalazine derivatives,[1] elemental analyses for compounds **5, 7, 9, 11, 13, 15** indicated partial hydration which could not be removed even on prolonged drying over P_2O_5 at 80°C/10^{-3} mbar. Therefore, accurate mass determinations were carried out to provide an additional proof for the molecular formulae.

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