

[4+2] CYCLOADDITION REACTIONS OF 1,4-BIS-(TRIFLUOROMETHYL)PYRIDO[3,4-*d*]PYRIDAZINE WITH INDOLE-TYPE DIENOPHILES¹

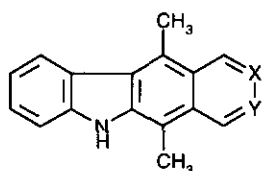
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Abstract - [4+2] Cycloaddition reactions of the title compound (**1**) with electron-rich indole-type dienophiles afford - besides different types of side products - tetracyclic compounds with a pyridocarbazole skeleton, structurally related to the alkaloid ellipticine or its isomer, isoellipticine. Three of the reaction products (compounds **4**, **5**, and **10**) were characterized by X-ray structure determination.

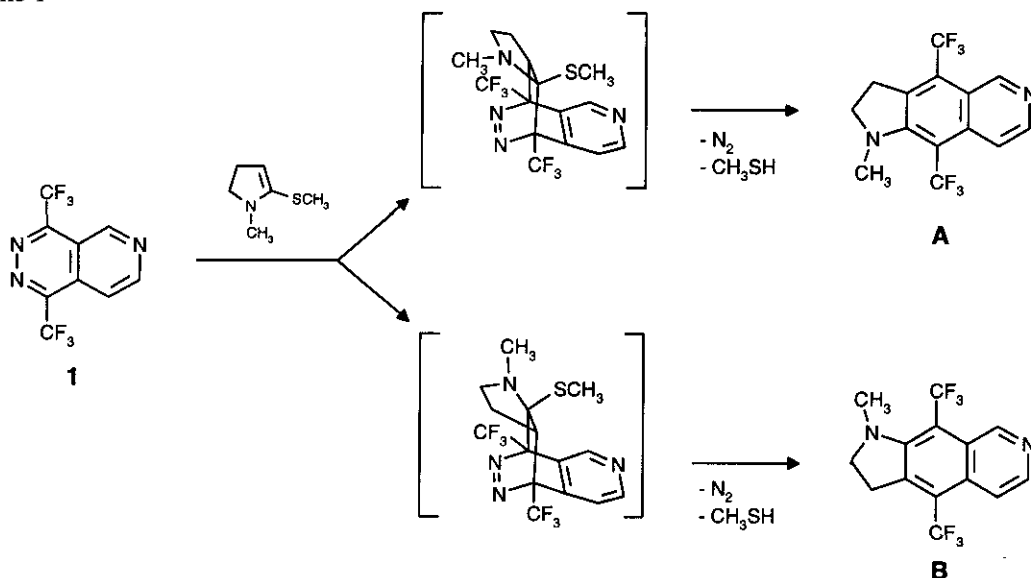
We have recently shown that employment of heterocycle-annelated pyridazines (such as pyridazino[4,5-*d*]pyridazines, pyrido[2,3-*d*]pyridazines, pyrido[3,4-*d*]pyridazines, or pyridazino[4,5-*b*]indoles) as azadienes in inverse-electron-demand Diels-Alder reactions can provide a convenient access to a wide variety of fused heterocyclic compounds.²⁻⁸ Based on the successful transformation of 1,4-bis(trifluoromethyl)pyrido[3,4-*d*]pyridazine (**1**) into *g*-annelated isoquinolines,⁵ we became interested in an extension of these investigations, aiming at the construction of tetracyclic systems of the pyridocarbazole type. In particular, the synthesis of fluorine-containing analogs of the alkaloid *ellipticine* (5,11-dimethyl-6*H*-pyrido[4,3-*b*]carbazole), which is attracting much attention due to its promising antitumor properties,⁹ was considered of pharmaceutical interest. The replacement of the two methyl groups in *ellipticine* by trifluoromethyl groups should cause relatively little change in the steric properties, but should have a marked influence on the electron distribution in the molecule as well as on its metabolism.



Ellipticine X = N, Y = CH
 Isoellipticine X = CH, Y = N

Our previous experiments⁵ with the azadiene (**1**) had shown that [4+2] cycloaddition reaction with the electron-rich ketene *N,S*-acetal, 1-methyl-2-methylthio-2-pyrroline gives rise to the formation of the two isomeric dihydropyrroloisoquinolines (**A**) and (**B**), which represent tricyclic partial structures of *ellipticine* and *isoellipticine*, respectively, in a ratio of **A** : **B** = 2.3 : 1 (Scheme 1).

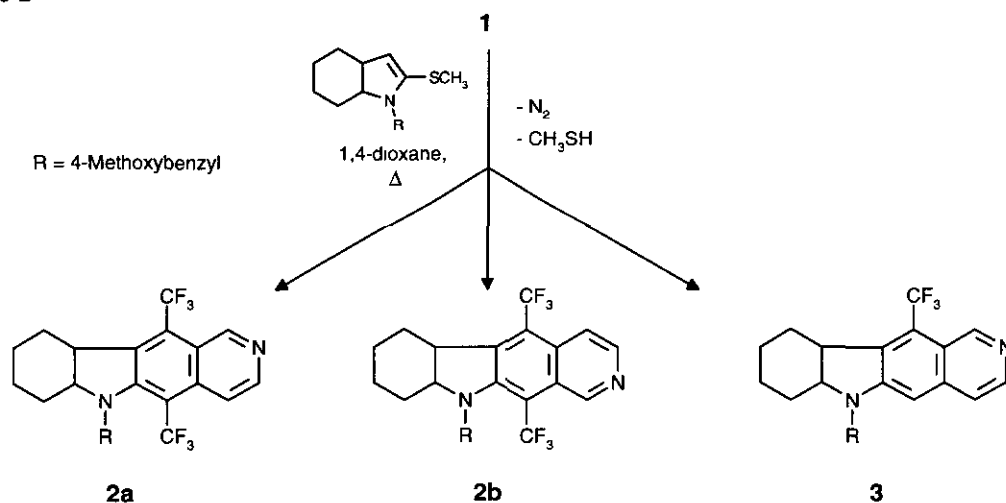
Scheme 1



Based on these findings, we now investigated the cycloaddition behavior of the pyrido[3,4-*d*]pyridazine (**1**) towards bicyclic dienophiles in order to build up the corresponding tetracyclic skeleton. For this purpose, a hexahydroindole-derived ketene *N,S*-acetal with an appropriate *N*-protecting group [i.e. 3a,4,5,6,7,7a-hexahydro-1-(4-methoxybenzyl)-2-methylthioindole; see Scheme 2] was considered a promising reagent. This dienophile had already been successfully used by *Neunhoeffer et al.* for the synthesis of *lavendamycin* analogs via an inverse-electron-demand Diels-Alder pathway.¹⁰ In this approach, the cyclohexane ring had been aromatized after the cycloaddition step, using 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) as oxidant.

When the azadiene (**1**) was treated with the ketene *N,S*-acetal [which was freshly prepared from 3a,4,5,6,7,7a-hexahydro-1-(4-methoxybenzyl)-2-methylthio-3*H*-indol-1-ium iodide^{10b}] in refluxing 1,4-dioxane, a complex reaction mixture was obtained from which three components could be isolated by medium-pressure liquid chromatography.¹¹ The first two fractions contained the expected isomeric pyridocarbazoles (**2a**) and (**2b**) in low yields of about 7% each.¹² The third fraction afforded a 20% yield of another tetracyclic compound which, surprisingly, was found to lack one of the two trifluoromethyl groups which were present in the starting material. So far, no acceptable mechanism can be proposed for this loss of a CF₃ moiety in compound (**3**) thus formed. On the other hand, the regiochemistry of the cycloaddition/cycloreversion reaction **1** → **3** [which determines the relative position of the pyridine nitrogen in compound (**3**)] unambiguously follows from nuclear Overhauser enhancement (nOe) spectroscopic experiments with **3**. A series of nOe difference signals (see Experimental) clearly indicates the close proximity of H-5 and H-4 as well as of H-5 and the CH₂ protons of the protecting group. Hence, the preferred relative orientation of azadiene and dienophile in the cycloaddition reaction must be the one which leads to bond formation between C-4 (and not C-1) of the pyrido[3,4-*d*]pyridazine and the more electron-rich sp² carbon atom (C-3) of the ketene acetal. This is in agreement with our previous observations in this series.⁵

Scheme 2

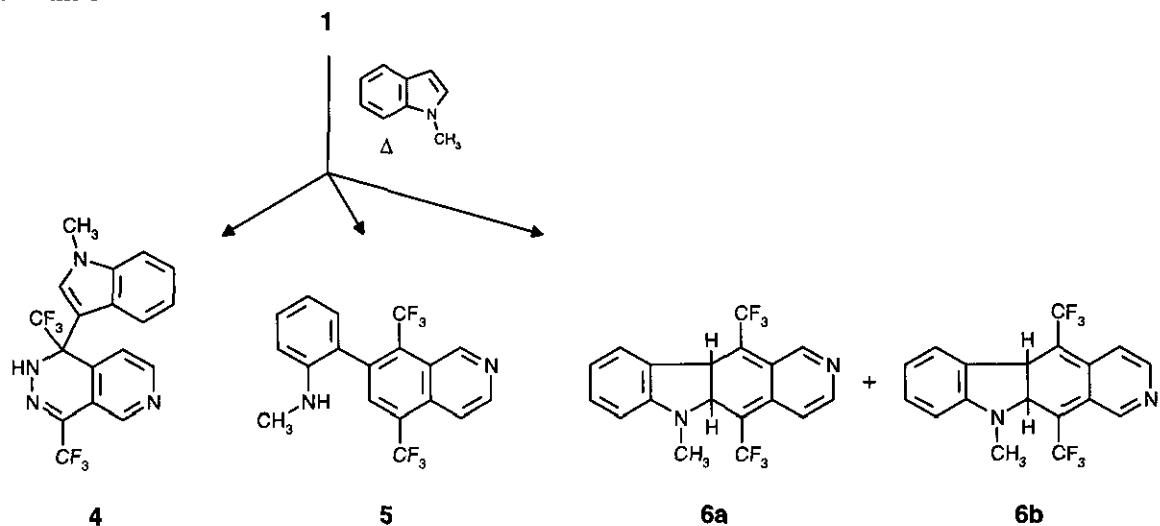


As a consequence of the low yields for the transformation **1** → **2a/2b**, we attempted an alternative approach to the tetracyclic target structures, consisting of a [4+2] cycloaddition reaction of the azadiene (**1**) with indole or *N*-methylindole, respectively, as the dienophile. The suitability of indole and some

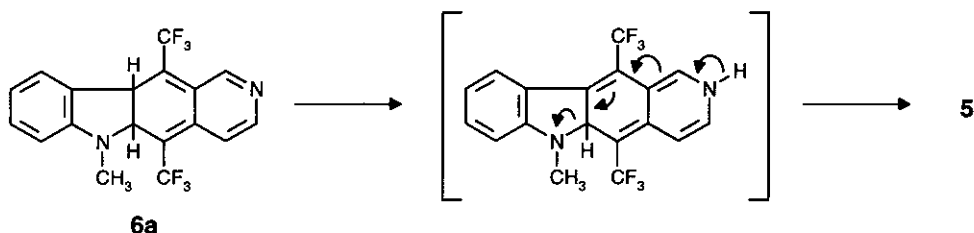
indole derivatives as electron-rich dienophiles in inverse-electron-demand Diels-Alder reactions has already been demonstrated by several research groups.¹³ With such a reagent, ring A of the resulting tetracycle would not require any subsequent dehydrogenation step, contrary to the case of the ketene *N,S*-acetal described above. On the other hand, the lack of an appropriate leaving group at the indole C-2 atom would lead - after cycloaddition and N₂ expulsion - to a product with a dihydropyridocarbazole structure which, in turn, had to be oxidized to the fully aromatic system.

Heating of the triazanaphthalene (**1**) in *N*-methylindole at 140°C afforded a mixture which was separated by column chromatography. Compound (**4**), isolated in 8% yield, obviously results from nucleophilic attack of the electron-rich indole C-3 atom at the pyridazine ring. The formation of similar side products in reactions of azadienes with indole derivatives has been reported previously.^{13c,e} In the case of compound (**5**) which was obtained in 22% yield, a cycloaddition reaction must have taken place, followed by ring opening of the five-membered substructure, thus leading to the trisubstituted isoquinoline displayed in Scheme 3. The structure of **5** as well as that of the addition product (**4**) could be firmly established by means of X-ray crystallography (see below for a discussion of the crystallographic findings). A mechanism for the formation of compound (**5**) from the initial cycloaddition product (**6a**), analogous to the pathway suggested for the cleavage of structurally related dihydropyridazino[4,5 *b*]-indole derivatives,^{13b,h} is proposed in Scheme 4.

Scheme 3

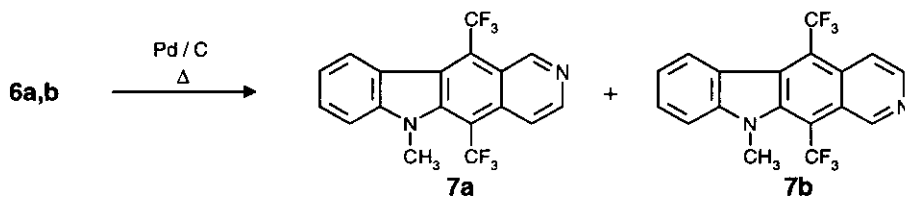


Scheme 4



The main fraction (yield: 37%) isolated from the cycloaddition reaction mixture was found to consist of the two isomeric dihydropyridocarbazoles (**6a**) and (**6b**) in a ratio of about 1:1. Owing to the very similar chromatographic behavior of the two components, any separation attempts failed so far. On the other hand, compounds (**6a,b**) could be dehydrogenated by refluxing in decaline in the presence of air oxygen and palladium on carbon as catalyst (Scheme 5). The resulting mixture of fully aromatic tetracycles (**7a**) and (**7b**), which represent hexafluoro derivatives of *N*-methyllellipticine and *N*-methylisoellipticine, again proved to be inseparable by crystallization as well as preparative liquid chromatography, whereas glc-ms analysis of the product mixture expectedly showed two chromatographic peaks with an almost identical ms fragmentation pattern (see Experimental).

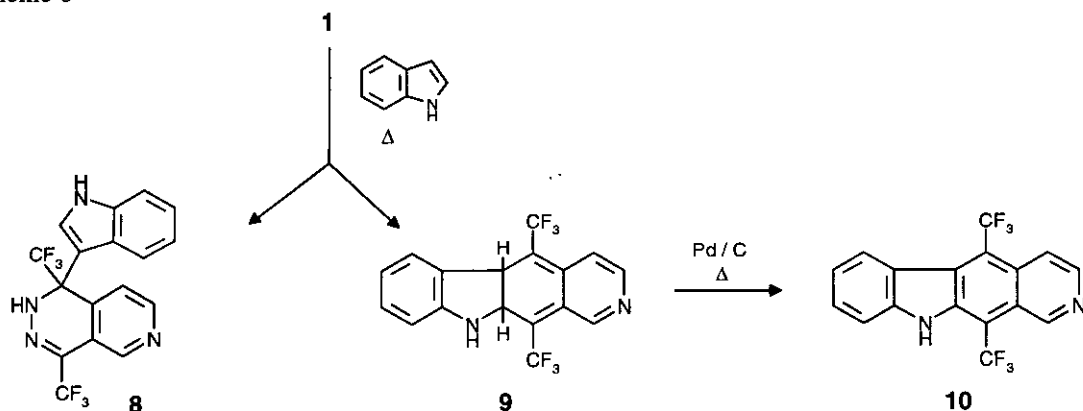
Scheme 5



When the pyrido[3,4-*d*]pyridazine (**1**) was heated to 140°C with 1.5 equivalents of indole in the absence of a solvent, the resulting mixture contained - besides substantial amounts of decomposition products - two isomerically pure reaction products in low yields which were isolated by column chromatography. For the compound eluted first, the structure of a 1,2-dihydro-1-(indol-3-yl)-1,4-bis(trifluoromethyl)pyrido[3,4-*d*]pyridazine (**8**) is proposed.¹⁴ Obviously, this dihydropyridopyridazine [like compound (**4**), see above] results from nucleophilic attack of the indole C-3 atom at the pyridazine ring of the starting material. The second fraction afforded a compound C₁₇H₁₀N₂F₆ for which, according to its elemental composition and spectral data, one of two possible isomeric structures of a dihydropyridocarbazole has to be formulated.¹⁵ This compound (**9**) could be conveniently dehydrogenated, again using palladium on

carbon in refluxing decaline, to afford the fully aromatic tetracyclic compound (**10**) in 52% yield (Scheme 6). The structure of a 5,11-bis(trifluoromethyl)-10*H*-pyrido[3,4-*b*]carbazole for **10** was unambiguously established by X-ray crystallography (see below) and is also in full agreement with micro-analytical and spectroscopic data (nmr, ms, ir); the hexafluoro compound (**10**) thus obtained represents a novel type of an *isoellipticine* analog.

Scheme 6



X-Ray Crystal Structure Determinations

Views of the molecular structures of compounds (**4**), (**5**), and (**10**) are shown in Figure 1, atomic parameters are given in Tables 1, 2, and 3. The structure of **4** contains a flat *N*-methylindole moiety with normal bond lengths and angles. In the dihydropyrido[3,4-*d*]pyridazine moiety, the pyridine ring is also flat while the dihydropyridazine ring adopts a conformation similar to a half-chair. The apex of this half-chair is formed by the sp^3 -type carbon atom C(6) which protrudes by 0.385(3) Å from the least-squares plane of the remaining five ring atoms. It is linked with the bulkier *N*-methylindole ligand in equatorial plane and with the C(25)F₃ group in axial position. The angle between the least-squares planes of the pyridine ring and the flat part of the pyridazine ring [C(5), N(7) through C(10)] is 9.6(1)°. The angles of these moieties with the indole plane are 81.3(1)° and 72.1(1)°, respectively. The bond lengths in the dihydropyridazine ring are consistent with a double bond N(8)-C(9) [1.291(2) Å], a single bond N(7)-N(8) [1.334(2) Å], and a single to double bond character for C(9)-C(10) [1.461(3) Å]. The N(7)-H(7) group forms a clearcut hydrogen bond to the pyridine nitrogen N(2) of a neighboring molecule, N(7)⋯N(2) = 2.912(2) Å, N(7)-H(7)⋯N(2) = 177(2)°.

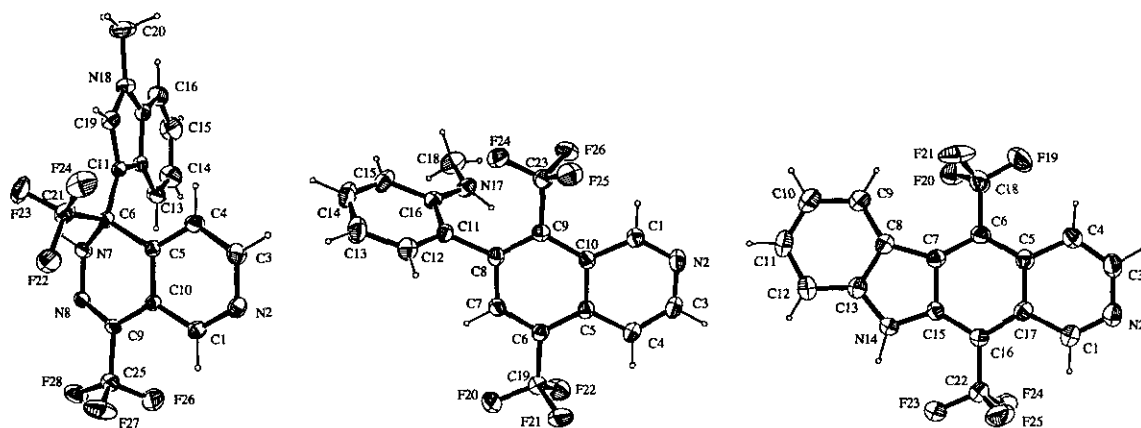


Figure 1. Crystal structures of **4**, **5**, and **10** (30% ellipsoids) and the numbering schemes employed for X-ray crystallographic data.

In compound (**5**), the isoquinoline and the aminophenyl moieties are essentially flat. Due to steric hindrance of the C(23)F₃ group, they are inclined at an angle of 70.2(1)°. The largest deviations from the least squares plane through the isoquinoline moiety are observed for the ring atom C(8) (0.050 Å) and the three substituent atoms C(11) (0.136 Å), C(19) (-0.126 Å), and C(23) (-0.060 Å). The corresponding figures for the aminophenyl residue are N(17), 0.041 Å, and C(18), 0.307 Å. In the unit cell the molecules are oriented with their isoquinoline moieties approximately parallel to each other and inclined at an angle of *ca.* 10° to (001). Neighboring molecules are linked *via* a relatively long hydrogen bond N(17)-H(17)...N(2) with N(17)-N(2) = 3.122(3) Å. In the case of compound (**10**), if one excludes the CF₃ groups from consideration, the molecule is flat, showing mean and maximum deviations of 0.027 Å and 0.099(3) Å [C(6)], respectively, from a common least-squares plane. Both CF₃ groups are distinctly bent off from this plane, the separations from the latter being 0.266(5) Å for C(18) and 0.105(4) Å for C(22). This unusual deformation is attributable to crystal packing effects. In the crystal lattice the molecules subtend with their mean planes an angle of about 30° with (001). Within the tetragonal unit cell they are arranged around the 4₂ axes in a fashion which gives rise to two different and relatively large but unfilled cavities. The CF₃ groups protrude into these cavities in a manner which supports their large out-of-plane bending [most pronounced for C(18)F₃]. The orientational disorder of the CF₃ groups - large for C(18)F₃ and small for C(22)F₃ - can be explained as an accompanying effect of this packing feature. Bond lengths and angles within the molecule are normal and compare reasonably well with those of carbazole,¹⁶ *N*-ethylcarbazole,¹⁷ and isoquinoline derivatives, e.g. compound (**5**). A hydrogen bond donated by the carbazole nitrogen N(14) and accepted by the isoquinoline nitrogen N(2), N(14)⋯N(2) = 2.967(4) Å, contributes to the coherence of the structure.

Table 1. Atomic coordinates and isotropic thermal displacement parameters for non-hydrogen atoms of compound (4), e.s.d.'s in parentheses.

| | <i>x/a</i> | <i>y/b</i> | <i>z/c</i> | <i>U</i> _{eq} [Å ²] |
|-------|------------|------------|------------|--|
| C(1) | 0.40808(8) | -0.0910(3) | 0.5187(1) | 0.0410(7) |
| N(2) | 0.39190(7) | -0.2031(2) | 0.4633(1) | 0.0503(6) |
| C(3) | 0.37661(9) | -0.1438(3) | 0.3906(1) | 0.0539(8) |
| C(4) | 0.37730(8) | 0.0273(3) | 0.3707(1) | 0.0431(7) |
| C(5) | 0.39492(7) | 0.1432(2) | 0.4283(1) | 0.0309(6) |
| C(6) | 0.40094(7) | 0.3321(2) | 0.4088(1) | 0.0316(6) |
| N(7) | 0.39972(6) | 0.4286(2) | 0.4837(1) | 0.0391(5) |
| N(8) | 0.41724(6) | 0.3736(2) | 0.55604(9) | 0.0364(6) |
| C(9) | 0.42429(7) | 0.2120(2) | 0.5671(1) | 0.0325(6) |
| C(10) | 0.41026(7) | 0.0852(2) | 0.5053(1) | 0.0310(6) |
| C(11) | 0.35923(7) | 0.4012(2) | 0.3507(1) | 0.0305(6) |
| C(12) | 0.30822(7) | 0.4463(2) | 0.3713(1) | 0.0333(6) |
| C(13) | 0.28159(8) | 0.4372(3) | 0.4409(1) | 0.0463(7) |
| C(14) | 0.23261(9) | 0.5020(4) | 0.4394(2) | 0.064(1) |
| C(15) | 0.20932(9) | 0.5760(4) | 0.3699(2) | 0.068(1) |
| C(16) | 0.23373(9) | 0.5848(3) | 0.3011(2) | 0.0580(9) |
| C(17) | 0.28314(8) | 0.5173(3) | 0.3019(1) | 0.0392(6) |
| N(18) | 0.31622(7) | 0.5126(2) | 0.2420(1) | 0.0446(6) |
| C(19) | 0.36146(8) | 0.4425(2) | 0.2720(1) | 0.0387(6) |
| C(20) | 0.3043(1) | 0.5676(4) | 0.1598(1) | 0.074(1) |
| C(21) | 0.45401(8) | 0.3580(3) | 0.3765(1) | 0.0493(8) |
| F(22) | 0.49125(4) | 0.3055(2) | 0.42969(9) | 0.0693(6) |
| F(23) | 0.46287(5) | 0.5223(2) | 0.36202(9) | 0.0734(6) |
| F(24) | 0.45936(5) | 0.2717(2) | 0.30921(9) | 0.0731(6) |
| C(25) | 0.44317(8) | 0.1627(3) | 0.6502(1) | 0.0468(8) |
| F(26) | 0.45053(5) | 0.2932(2) | 0.69907(7) | 0.0646(5) |
| F(27) | 0.48709(6) | 0.0783(2) | 0.65129(9) | 0.0850(6) |
| F(28) | 0.41053(7) | 0.0585(2) | 0.68403(8) | 0.0936(7) |

Table 2. Atomic coordinates and isotropic thermal displacement parameters for non-hydrogen atoms of compound (5).

| | <i>x/a</i> | <i>y/b</i> | <i>z/c</i> | <i>U</i> _{eq} [Å ²] |
|-------|------------|------------|------------|--|
| C(1) | 0.2399(2) | 0.2157(1) | 0.1796(3) | 0.050(1) |
| N(2) | 0.2880(2) | 0.1461(1) | 0.1985(3) | 0.059(1) |
| C(3) | 0.3909(2) | 0.1480(1) | 0.2565(3) | 0.059(1) |
| C(4) | 0.4470(2) | 0.2167(1) | 0.2893(3) | 0.049(1) |
| C(5) | 0.3965(2) | 0.2925(1) | 0.2662(3) | 0.038(1) |
| C(6) | 0.4486(2) | 0.3684(1) | 0.2936(3) | 0.039(1) |
| C(7) | 0.3932(2) | 0.4383(1) | 0.2789(3) | 0.041(1) |
| C(8) | 0.2840(2) | 0.4408(1) | 0.2337(3) | 0.037(1) |
| C(9) | 0.2322(2) | 0.3687(1) | 0.1947(3) | 0.037(1) |
| C(10) | 0.2878(2) | 0.2932(1) | 0.2123(3) | 0.038(1) |
| C(11) | 0.2370(2) | 0.5239(1) | 0.2306(3) | 0.039(1) |
| C(12) | 0.2577(2) | 0.5780(1) | 0.0997(3) | 0.054(1) |
| C(13) | 0.2184(2) | 0.6561(1) | 0.0916(4) | 0.066(1) |
| C(14) | 0.1579(2) | 0.6790(2) | 0.2180(4) | 0.066(1) |
| C(15) | 0.1378(2) | 0.6273(1) | 0.3537(3) | 0.056(1) |
| C(16) | 0.1784(2) | 0.5485(1) | 0.3646(3) | 0.042(1) |
| N(17) | 0.1606(1) | 0.4956(1) | 0.5000(3) | 0.049(1) |
| C(18) | 0.1161(2) | 0.5238(2) | 0.6561(3) | 0.071(1) |
| C(19) | 0.5645(2) | 0.3716(1) | 0.3390(3) | 0.051(1) |
| F(20) | 0.6002(1) | 0.44723(8) | 0.3470(2) | 0.0775(6) |
| F(21) | 0.6120(1) | 0.33337(9) | 0.2171(2) | 0.0746(6) |
| F(22) | 0.5982(1) | 0.33765(9) | 0.4978(2) | 0.0766(6) |
| C(23) | 0.1172(2) | 0.3652(1) | 0.1307(3) | 0.046(1) |
| F(24) | 0.0720(1) | 0.43667(8) | 0.1002(2) | 0.0571(5) |
| F(25) | 0.0973(1) | 0.32415(8) | -0.0251(2) | 0.0680(6) |
| F(26) | 0.0666(1) | 0.32681(8) | 0.2497(2) | 0.0651(6) |

Table 3. Atomic coordinates and isotropic thermal displacement parameters for compound (10); F sites with low occupation factors and H atoms omitted.

| | <i>x/a</i> | <i>y/b</i> | <i>z/c</i> | <i>U</i> _{eq} [Å ²] |
|--------------------|------------|------------|------------|--|
| C(1) | 0.5277(2) | 0.2575(2) | 0.5362(4) | 0.059(1) |
| N(2) | 0.4853(2) | 0.2152(1) | 0.6160(3) | 0.067(1) |
| C(3) | 0.4166(2) | 0.2364(2) | 0.6279(4) | 0.071(2) |
| C(4) | 0.3897(2) | 0.2956(2) | 0.5617(4) | 0.062(1) |
| C(5) | 0.4344(2) | 0.3423(2) | 0.4725(4) | 0.048(1) |
| C(6) | 0.4111(2) | 0.4059(2) | 0.3970(4) | 0.049(1) |
| C(7) | 0.4596(2) | 0.4508(2) | 0.3243(3) | 0.044(1) |
| C(8) | 0.4555(2) | 0.5195(2) | 0.2433(4) | 0.046(1) |
| C(9) | 0.4019(2) | 0.5701(2) | 0.2169(4) | 0.060(1) |
| C(10) | 0.4178(2) | 0.6306(2) | 0.1332(4) | 0.072(2) |
| C(11) | 0.4855(2) | 0.6423(2) | 0.0740(4) | 0.070(1) |
| C(12) | 0.5399(2) | 0.5946(2) | 0.0993(4) | 0.062(1) |
| C(13) | 0.5239(2) | 0.5339(2) | 0.1864(4) | 0.049(1) |
| N(14) | 0.5697(1) | 0.4795(1) | 0.2291(3) | 0.051(1) |
| C(15) | 0.5332(2) | 0.4288(2) | 0.3134(4) | 0.044(1) |
| C(16) | 0.5568(2) | 0.3652(2) | 0.3769(4) | 0.047(1) |
| C(17) | 0.5074(2) | 0.3225(2) | 0.4614(4) | 0.046(1) |
| C(18) | 0.3333(2) | 0.4259(3) | 0.3921(6) | 0.081(2) |
| C(22) | 0.6315(2) | 0.3399(2) | 0.3553(5) | 0.065(1) |
| F(19) ⁺ | 0.2873(2) | 0.3812(3) | 0.4451(7) | 0.139(3) |
| F(20) ⁺ | 0.3132(2) | 0.4415(2) | 0.2437(4) | 0.081(1) |
| F(21) ⁺ | 0.3215(2) | 0.4878(3) | 0.4785(4) | 0.110(2) |
| F(23) ⁺ | 0.6714(1) | 0.3835(1) | 0.2703(4) | 0.106(1) |
| F(24) ⁺ | 0.6339(1) | 0.2770(1) | 0.2784(3) | 0.093(1) |
| F(25) ⁺ | 0.6662(1) | 0.3289(2) | 0.4914(3) | 0.090(1) |

⁺ CF₃ groups exhibit orientation disorder with site occupation factor *pp1* = 0.774(7) for F(19) through F(21), *pp2* = 0.963(4) for F(23) through F(25).

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage microscope and are uncorrected. Ir spectra were recorded for KBr pellets on a Perkin-Elmer 1605 FT-IR instrument; ¹H-nmr spectra were recorded on a Varian Unityplus 300 (300 MHz), a Bruker AM 400 WB (400 MHz), or a Bruker AC 80 (80 MHz) spectrometer (TMS as internal reference, δ values in ppm). Mass spectra were obtained with a Hewlett-Packard 5890A/5970B-GC/MSD spectrometer (glc column: HP-1, 12 m x 0.2 mm x 0.33 μm); exact mass determinations were performed by Ing. J. Dolezal at the Institute of General Chemistry, Technical University of Vienna, using a Finnigan MAT 8230 spectrometer (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). Light petroleum refers to the fraction of bp 50-70°C. For X-ray data collection, a Philips PW1100 diffractometer was employed (Mo Kα radiation, λ = 0.71069 Å) and the programs SHELX76¹⁸ and XTAL3.2¹⁹ were used for crystallographic calculations. Microanalyses were performed at the Institute of Physical Chemistry (Microanalytical Laboratory), University of Vienna.

Reaction of 1,4-Bis(trifluoromethyl)pyrido[3,4-*d*]pyridazine (1) with 3a,4,5,6,7,7a-Hexahydro-1-(4-methoxybenzyl)-2-methylthioindole

To a solution of 3a,4,5,6,7,7a-hexahydro-1-(4-methoxybenzyl)-2-methylthio-3*H*-indol-1-ium iodide^{10b} (500 mg, 1.2 mmol) in dry ether (5 ml) was added potassium *tert*-butoxide (168 mg, 1.5 mmol), and the mixture was refluxed for 3 h under an argon atmosphere. The precipitate (potassium iodide) was filtered off and the volatile components were removed under reduced pressure. The residue was dissolved in dry 1,4-dioxane (6 ml). After addition of 1,4-bis(trifluoromethyl)pyrido[3,4-*d*]pyridazine⁵ (1) (267 mg, 1 mmol), the solution was refluxed for 20 min under an argon atmosphere. The solvent was removed and the residue was subjected to mplc (dichloromethane/ethyl acetate, 19:1). The first fraction contained 33 mg (7%) of 6a,7,8,9,10,10a-hexahydro-6-(4-methoxybenzyl)-5,11-bis(trifluoromethyl)-6*H*-pyrido[4,3-*b*]carbazole (2a) or 5b,6,7,8,9,9a-hexahydro-10-(4-methoxybenzyl)-5,11-bis(trifluoromethyl)-10*H*-pyrido[3,4-*b*]carbazole (2b), respectively, as a yellow oil which slowly crystallized, mp 62-64°C. Exact Mass Calcd for C₂₅H₂₂N₂OF₆ (M⁺): 480.1636. Found: 480.1643. Ms: *m/z* (rel. int.) 482 (19%), 481 (90), 480 (M⁺, 92), 479 (71), 478 (37), 426 (33), 425 (34), 424 (25), 423 (11), 360 (14), 359 (25), 358 (25), 357 (20), 356 (12), 331 (11), 330 (13), 329 (12), 318 (12), 317 (15), 316 (16), 309 (11), 152 (13), 151 (10), 135 (27), 134 (19), 122 (46), 121 (100), 91 (11), 78 (11), 77 (20), 76 (12). ¹H-Nmr (80 MHz, CDCl₃) δ: 9.36 (unresolved, 1 H, H-1), 8.45 (d, *J* = 6.0 Hz, 1 H, H-3), 8.00-7.70 (m, 1 H, H-4), 7.13 (d, *J* = 8.7 Hz, 2 H, phenyl-H), 7.00-6.70 (m, 2 H, phenyl-H), 4.58 (s, 2 H, benzyl-H), 3.90-3.30 (s and m, 4 H, OCH₃, H-6a or H-9a, respectively), 2.40-1.00 (m, 9 H, cyclohexane-H). Evaporation of the second fraction gave 38 mg (8%) of 5b,6,7,8,9,9a-hexahydro-10-(4-methoxybenzyl)-5,11-bis(trifluoromethyl)-10*H*-pyrido[3,4-*b*]carbazole (2b) or 6a,7,8,9,10,10a-hexahydro-6-(4-methoxybenzyl)-5,11-bis(trifluoromethyl)-6*H*-pyrido[4,3-*b*]carbazole (2a), respectively, as a yellow oil which slowly crystallized, mp 147-150°C. Exact Mass Calcd for C₂₅H₂₂N₂OF₆ (M⁺): 480.1636. Found: 480.1636. Ms: *m/z* (rel. int.) 480 (M⁺, 26%), 425 (12), 122 (35), 121 (100), 91 (10), 77 (13). ¹H-Nmr (80 MHz, CDCl₃) δ: 9.31 (unresolved, 1 H, H-1), 8.48 (d, *J* = 6.0 Hz, 1 H, H-3), 7.90-7.60 (m, 1 H, H-4), 7.10 (d, *J* = 8.7 Hz, 2 H, phenyl-H), 7.00-6.70 (m, 2 H, phenyl-H), 4.83-4.39 (AB system, *J* = 16.0 Hz, 2 H, benzyl-H), 3.77 (s, 3 H, OCH₃), 3.80-3.40 (m, 1 H, H-9a or H-6a, respectively), 2.20-1.00 (m, 9 H, cyclohexane-H). The third fraction contained 81 mg (20%) of 6a,7,8,9,10,10a-hexahydro-6-(4-methoxybenzyl)-11-trifluoromethyl-6*H*-pyrido[4,3-*b*]carbazole (3) as a yellow oil which slowly crystallized, mp 129-131°C. Exact Mass Calcd for C₂₄H₂₃N₂OF₃ (M⁺): 412.1762. Found: 412.1762. Anal. Calcd for C₂₄H₂₃N₂OF₃ · 0.5 H₂O: C, 68.40; H, 5.74; N, 6.65. Found: C, 68.46; H, 5.37; N, 6.43. Ms: *m/z* (rel. int.) 412 (M⁺, 13%), 122 (10), 121 (100). ¹H-Nmr (80 MHz, CDCl₃) δ: 9.27 (q, *J*_{H-F} = 2.4 Hz, 1 H, H-1), 8.34 (d, *J* = 5.7 Hz,

1 H, H-3), 7.50-7.10 (m, 3 H, H-4, phenyl-H; the signal portion of H-4 shows a positive nOe on irradiation at 6.65 ppm), 7.00-6.75 (m, 2 H, phenyl-H), 6.65 (s, 1 H, H-5; shows a positive nOe on saturation of the benzyl-H resonances at 4.73-4.10 ppm), 4.73-4.10 (AB system, $J = 16.2$ Hz, 2 H, benzyl-H; shows a positive nOe on irradiation at 6.65 ppm), 3.80 (s, 3 H, OCH₃), 3.80-3.40 (m, 1 H, H-6a), 2.40-1.10 (m, 9 H, cyclohexane-H).

Reaction of 1,4-Bis(trifluoromethyl)pyrido[3,4-*d*]pyridazine (1) with *N*-Methylindole

A solution of **1** (534 mg, 2 mmol) in *N*-methylindole (2.5 ml, 19.5 mmol) was heated to 140°C for 3 h. Volatile components were removed by Kugelrohr distillation and the residue was subjected to column chromatography (light petroleum/ethyl acetate, 17:3 → 1:1). Evaporation of the first fraction gave 163 mg (22%) of 7-(2-methylaminophenyl)-5,8-bis(trifluoromethyl)isoquinoline (**5**) as red crystals, mp 142-143°C (ethanol). *Anal.* Calcd for C₁₈H₁₂N₂F₆: C, 58.39; H, 3.27; N, 7.57. Found: C, 58.12; H, 3.11; N, 7.30. Ms: m/z (rel. int.) 371 (20%), 370 (M⁺, 100), 331 (21), 301 (33), 286 (43). Ir (cm⁻¹): 3342 (NH). ¹H-Nmr (80 MHz, CDCl₃) δ: 9.85-9.70 (m, 1 H, H-1), 8.80 (d, $J = 6.1$ Hz, 1 H, H-3), 8.15-7.90 (m, 2 H, H-4, H-6), 7.55-7.25 (m, 1 H, phenyl-H), 7.10-6.70 (m, 3 H, phenyl-H), 3.16 (t, unresolved, 1 H, NH; exchangeable with D₂O), 2.83 (d, $J = 4.9$ Hz, s after D₂O exchange, 3 H, CH₃). The second fraction contained 64 mg (8%) of 1,2-dihydro-1-(1-methylindol-3-yl)-1,4-bis(trifluoromethyl)pyrido[3,4-*d*]pyridazine (**4**) as colorless needles, mp 212-215°C (CHCl₃). *Anal.* Calcd for C₁₈H₁₂N₄F₆: C, 54.28; H, 3.04; N, 14.07. Found: C, 54.46; H, 2.96; N, 13.86. Ms: m/z (rel. int.) 398 (M⁺, 18%), 330 (19), 329 (100), 131 (13). ¹H-Nmr (400 MHz, DMSO-*d*₆) δ: 10.07 (s, 1 H, NH; exchangeable with D₂O), 8.71 (s, 1 H, H-5), 8.57 (d, $J = 5.4$ Hz, 1 H, H-7), 7.71 (s, 1 H, indole H-2), 7.52 (d, $J = 7.9$ Hz, 1 H, indole H-7), 7.22-7.14 (m, 1 H, indole H-6), 7.00-6.90 (m, 2 H, H-8, indole H-5), 6.85 (d, $J = 7.9$ Hz, 1 H, indole H-4), 3.90 (s, 3 H, CH₃). Evaporation of the third fraction afforded 274 mg (37%) of a mixture of 5a,10b-dihydro-6-methyl-5,11-bis(trifluoromethyl)-6*H*-pyrido[4,3-*b*]carbazole (**6a**) and 5a,10a-dihydro-10-methyl-5,11-bis(trifluoromethyl)-10*H*-pyrido[3,4-*b*]carbazole (**6b**) as a yellow powder. *Anal.* Calcd for C₁₈H₁₂N₂F₆: C, 58.39; H, 3.27; N, 7.57. Found: C, 58.25; H, 3.12; N, 7.40. Glc-ms: peak 1, m/z (rel. int.) 371 (13%), 370 (M⁺, 58), 302 (20), 301 (97), 233 (18), 232 (100), 231 (28), 217 (14), 116 (11); peak 2, m/z (rel. int.) 370 (M⁺, 45%), 302 (20), 301 (100), 233 (12), 232 (65), 231 (19), 116 (16). ¹H-Nmr (80 MHz, CDCl₃) δ: 9.05-8.80 (m, 1 H, H-1), 8.69 (d, $J = 5.2$ Hz, 1 H, H-3), 7.90-7.10 (m, 5 H, H-4, benzene-H), 5.35-4.75 (m, 2 H, H-5a, H-10a and H-5a, H-10b, respectively), 3.86 (s, 3 H, CH₃).

6-Methyl-5,11-bis(trifluoromethyl)-6H-pyrido[4,3-b]carbazole (7a) and 10-Methyl-5,11-bis(trifluoromethyl)-10H-pyrido[3,4-b]carbazole (7b)

To the mixture (see above) of compounds (6a) and (6b) (80 mg, 0.22 mmol) in decaline (5 ml) was added 10% Pd/C catalyst (80 mg), and the solution was refluxed with vigorous stirring for 20 h. The solvent was removed by Kugelrohr distillation, and the residue was repeatedly extracted with boiling ethyl acetate and methanol. The combined extracts were filtered hot, then the solvent was evaporated. Column chromatography (light petroleum/ethyl acetate, 4:1) afforded 30 mg (37%) of a mixture (1:1, according to $^1\text{H-Nmr}$) of compounds (7a) and (7b) as a yellow powder. *Anal.* Calcd for $\text{C}_{18}\text{H}_{10}\text{N}_2\text{F}_6$: C, 58.70; H, 2.74; N, 7.61. Found: C, 58.94; H, 2.66; N, 7.37. Glc-ms: peak 1, m/z (rel. int.) 369 (20%), 368 (M^+ , 100), 353 (19); peak 2, m/z (rel. int.) 369 (20%), 368 (M^+ , 100), 367 (10), 353 (16). $^1\text{H-Nmr}$ (300 MHz, CDCl_3) δ : 9.80 and 9.71 (br s, 1 H, H-1), 8.65-8.45 and 8.45-8.35 (m, 2 H, H-3, H-10 or H-6, respectively), 8.23-8.13 and 8.07-7.95 (m, 1 H, H-4), 7.75-7.55 (m, 1 H, H-8), 7.45-7.25 (m, 2 H, H-7, H-9), 4.00-3.75 (m, 3 H, CH_3).

Reaction of 1,4-Bis(trifluoromethyl)pyrido[3,4-d]pyridazine (1) with Indole

A finely ground mixture of **1** (801 mg, 3 mmol) and indole (526 mg, 4.5 mmol) was fused and kept at 140°C for 1.5 h, then it was cooled and subjected to column chromatography (dichloromethane/ethyl acetate, 9:1, then light petroleum/ethyl acetate, 1:1). The first fraction contained 115 mg (10%) of 1,2-dihydro-1-(indol-3-yl)-1,4-bis(trifluoromethyl)pyrido[3,4-d]pyridazine (**8**) as colorless crystals, mp 240°C (decomp.; ethanol). *Anal.* Calcd for $\text{C}_{17}\text{H}_{10}\text{N}_4\text{F}_6$: C, 53.13; H, 2.62; N, 14.58. Found: C, 53.24; H, 2.67; N, 14.34. Ms: m/z (rel. int.) 384 (M^+ , 15%), 316 (18), 315 (100), 314 (39), 157 (13), 117 (36), 116 (16). Ir (cm^{-1}): 3390 (NH). $^1\text{H-Nmr}$ (400 MHz, $\text{DMSO}-d_6$) δ : 11.63 (s, 1 H, NH; exchangeable with D_2O), 10.07 (s, 1 H, NH; exchangeable with D_2O), 8.71 (s, 1 H, H-5), 8.57 (d, $J = 5.2$ Hz, 1 H, H-7), 7.68-7.60 (m, 1 H, indole H-2), 7.48 (d, $J = 8.4$ Hz, 1 H, indole H-7), 7.15-7.07 (m, 1 H, indole H-6), 6.96 (d, $J = 5.2$ Hz, 1 H, H-8), 6.93-6.82 (m, 2 H, indole H-4, H-5). Evaporation of the second fraction afforded 170 mg (16%) of 5a,10a-dihydro-5,11-bis(trifluoromethyl)-10H-pyrido[3,4-b]carbazole (**9**) as almost colorless crystals, mp $222-224^\circ\text{C}$ (decomp.; light petroleum/ethyl acetate). *Anal.* Calcd for $\text{C}_{17}\text{H}_{10}\text{N}_2\text{F}_6$: C, 57.31; H, 2.83; N, 7.86. Found: C, 57.44; H, 2.99; N, 7.69. Ms: m/z (rel. int.) 357 (11%), 356 (M^+ , 56), 288 (19), 287 (100), 267 (31), 218 (27). Ir (cm^{-1}): 3184 (NH). $^1\text{H-Nmr}$ (80 MHz, $\text{CDCl}_3/\text{DMSO}-d_6$) δ : 11.39 (s, 1 H, NH), 8.80 (s, 1 H, H-1), 8.60 (d, $J = 5.1$ Hz, 1 H, H-3), 7.80-6.95 (m, 5 H, H-4, H-6, H-7, H-8, H-9), 5.40-5.00 (m, 2 H, H-5a, H-10a).

5,11-Bis(trifluoromethyl)-10H-pyrido[3,4-b]carbazole (10)

Compound (9) (100 mg, 0.28 mmol) was refluxed with 10% Pd/C catalyst (100 mg) in decaline (5 ml) for 36 h with vigorous stirring. The solvent was removed by Kugelrohr distillation, and the residue was repeatedly extracted with boiling ethyl acetate and methanol. The combined extracts were filtered hot, then the solvent was evaporated. Column chromatography (light petroleum/ethyl acetate, 4:1) afforded 52 mg (52%) of 10 as yellow needles, mp 249-251°C (ethanol). *Anal.* Calcd for C₁₇H₈N₂F₆: C, 57.64; H, 2.28; N, 7.91. Found: C, 57.35; H, 2.03; N, 7.72. Ms: *m/z* (rel. int.) 355 (20%), 354 (M⁺, 100), 335 (19), 334 (67), 333 (13), 315 (11), 314 (11), 265 (15). Ir (cm⁻¹): 3154 (NH). ¹H-Nmr (300 MHz, CDCl₃) δ: 9.72 (q, *J*_{H-F} = 1.5 Hz, 1 H, H-1), 8.92 (br s, 1 H, NH), 8.57 (d, *J* = 6.3 Hz, 1 H, H-3), 8.46-8.39 (m, 1 H, H-6), 8.26 (dq, *J* = 6.3 Hz, *J*_{H-F} = 1.2 Hz, 1 H, H-4), 7.62-7.54 (m, 1 H, H-8), 7.49-7.43 (m, 1 H, H-9), 7.32-7.25 (m, 1 H, H-7).

X-Ray Structure Determination of Compound (4)²⁰

C₁₈H₁₂F₆N₄, *M_r* = 398.31, monoclinic, C2/c (No. 15), *a* = 26.135(4) Å, *b* = 7.835(2) Å, *c* = 16.711(4) Å, β = 94.04(1)°, *V* = 3413(1) Å³, *Z* = 8, *D_c* = 1.550 g cm⁻³, μ = 0.134 mm⁻¹, *F*(000) = 1616, *T* = 25 °C. A colorless prism (0.22 x 0.23 x 0.65 mm) was used for data collection. Of 3350 reflections collected (Θ-2Θ scans, Θ_{max} = 25°, correction for LP, absorption neglected), 3004 were independent and 2164 [*F* > 6σ(*F*)] were used for least-squares refinement after solving the structure with direct methods. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were inserted in idealized positions and refined with constraints (riding model for aromatic H, rigid group for CH₃, no constraint for N-bonded H). Final *R* = 0.037, *wR* = 0.041, and *S* = 1.63; final difference Fourier map showed minimum and maximum values of -0.19 and +0.17 e Å⁻³.

X-Ray Structure Determination of Compound (5)²⁰

C₁₈H₁₂N₂F₆, *M_r* = 370.30, monoclinic, P2₁/c (No. 14), *a* = 13.031(2) Å, *b* = 16.496(3) Å, *c* = 7.485(1) Å, β = 97.99(1)°, *V* = 1593.4(4) Å³, *Z* = 4, *D_c* = 1.544 g cm⁻³, μ = 0.135 mm⁻¹, *F*(000) = 752, *T* = 25 °C. A red prism (0.20 x 0.21 x 0.55 mm) was used for data collection. Of 3134 reflections collected (Θ-2Θ scans, Θ_{max} = 25°, correction for LP, absorption neglected), 2801 were independent and 1801 [*F* > 6σ(*F*)] were used for least-squares refinement after solving the structure with direct methods. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included in idealized positions (C-H = 0.96 Å) and were then refined with constraints (riding model for aromatic H, rigid group for CH₃,

unconstrained for N-bonded H). Final $R = 0.035$, $wR = 0.039$, and $S = 1.43$; final difference Fourier map showed minimum and maximum values of -0.17 and $+0.16 \text{ e } \text{Å}^{-3}$.

X-Ray Structure Determination of Compound (10)²⁰

$\text{C}_{17}\text{H}_8\text{N}_2\text{F}_6$, $M_r = 345.25$, tetragonal, $P4_2/n$ (No. 86), $a = 18.770(2) \text{ Å}$, $c = 8.405(2) \text{ Å}$, $V = 2961.2(9) \text{ Å}^3$, $Z = 8$, $D_c = 1.589 \text{ g cm}^{-3}$, $\mu = 0.102 \text{ mm}^{-1}$, $F(000) = 1424$, $T = 24^\circ\text{C}$. A yellow prism ($0.20 \times 0.20 \times 0.45 \text{ mm}$) was used for data collection. Of 2776 reflections collected (Θ - 2Θ scans, $\Theta_{\text{max}} = 25^\circ$, correction for LP, absorption neglected), 2603 were independent and 1390 [$F > 6\sigma(F)$] were used for least-squares refinement after solving the structure with direct methods. All non-hydrogen atoms were refined anisotropically, except for six partly occupied F sites of the two CF_3 groups which were found to show an orientational disorder (rotation by about 180° about the C- CF_3 bond axes). Hydrogen atoms were inserted in idealized positions (C-H = 0.96 Å) and were refined with the riding model. Final $R = 0.041$, $wR = 0.042$, and $S = 1.49$; final difference Fourier map showed minimum and maximum values of -0.23 and $+0.21 \text{ e } \text{Å}^{-3}$.

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11. Carrying out this reaction at room temperature gave the same product mixture, yet the yields of **2a**, **2b**, and **3** were slightly lower.
12. So far, no structural assignment can be made with respect to the regioisomerism of the two isolated hexahydropyridocarbazoles of type **2**, as the crystals of both isomers were not suitable for an X-ray crystal structure determination.
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14. Although the structure of an isomeric 3,4-dihydro-4-(indol-3-yl)-1,4-bis(trifluoromethyl)pyrido[3,4-*d*]pyridazine cannot be excluded for compound (**8**) (X-ray data could not be obtained), the close resemblance of the ¹H-nmr spectrum with that of the *N*-methyl analog (**4**) suggests the structure shown in Scheme 6.
15. The formation of a pyrido[4,3-*b*]carbazole isomer besides the pyrido[3,4-*b*]carbazole (**9**) in the cycloaddition of **1** and indole cannot be ruled out, although we could not isolate such a compound from the reaction mixture nor did we find a corresponding ring-opened product (i.e. an analog to **5**).
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20. Lists of crystallographic data and experimental information, atomic coordinates, anisotropic thermal parameters, bond lengths and angles, least-squares planes, and observed and calculated structure factors have been deposited with the Cambridge Crystallographic Data Centre, U.K.

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