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NEW SYNTHESIS OF MODEL DIHYDROAZEPINE-FUSED INDOLO[2,3-*c*]QUINOLINES

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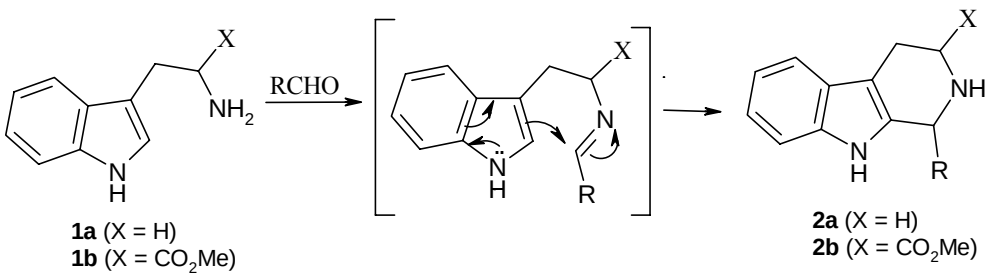
Abstract– A synthetic route involving double Pictet-Spengler condensations at the indolic C-2 and C- 4 positions of a 3-diaminophenylindole **(8)** is described leading to a novel dihydroazepine-fused indoloquinoline system. MS and NMR spectral data are in accordance with the assigned pentacyclic structures namely, 7,8-dihydro-1,12-iminobenzo[*c*]pyrido[4,3,2-*ef*][1]benzazepines **(9a,b)**, as confirmed by X-Ray measurements.

INTRODUCTION

The Pictet-Spengler condensation reaction of indole bases, such as tryptamines **(1a)** and tryptophan esters **(1b)**, with various aldehydes constitutes a versatile synthetic route towards numerous 1,2,3,4-tetrahydro-*β*-carbolines **(**e.g. **2a,b)** (Scheme 1). This one-pot reaction, conducted under the classical conditions of acid catalysis[1] (**1a→2a**) or in nonacidic aprotic media [2,3] (**1b→2b**), is widely applicable in the synthesis of indole alkaloids of more complex structure, and the subject has recently been reviewed.[4] The electrophilic nature of the initially formed imine double bond provides the driving force for attack of

Scheme 1



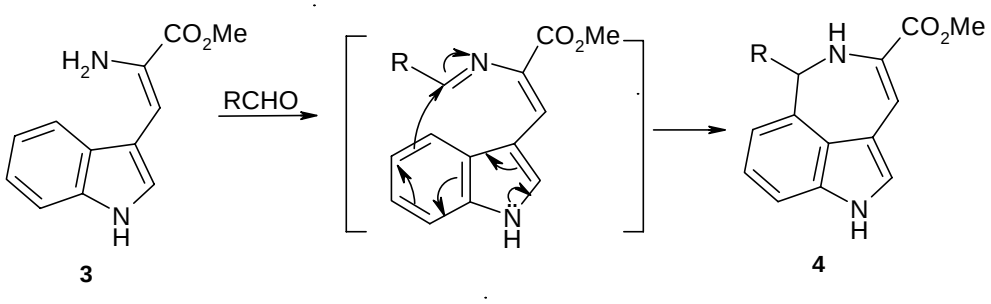
1a (X = H)
1b (X = CO_2Me)

2a (X = H)
2b (X = CO_2Me)

the indolic C2 - C3 double bond and consequent cyclization which usually rests regioselectively at the C-2 locus. [2,5]

On the other hand, the acid-catalyzed condensation of dehydrotryptophan ester (**3**) with aldehydes was reported to yield the respective 5,6-dihydroazepino[5,4,3-*cd*]indoles (**4**) as the major products, implying that cyclization occurred regioselectively at the indolic C- 4 position (Scheme 2). [6]

Scheme 2



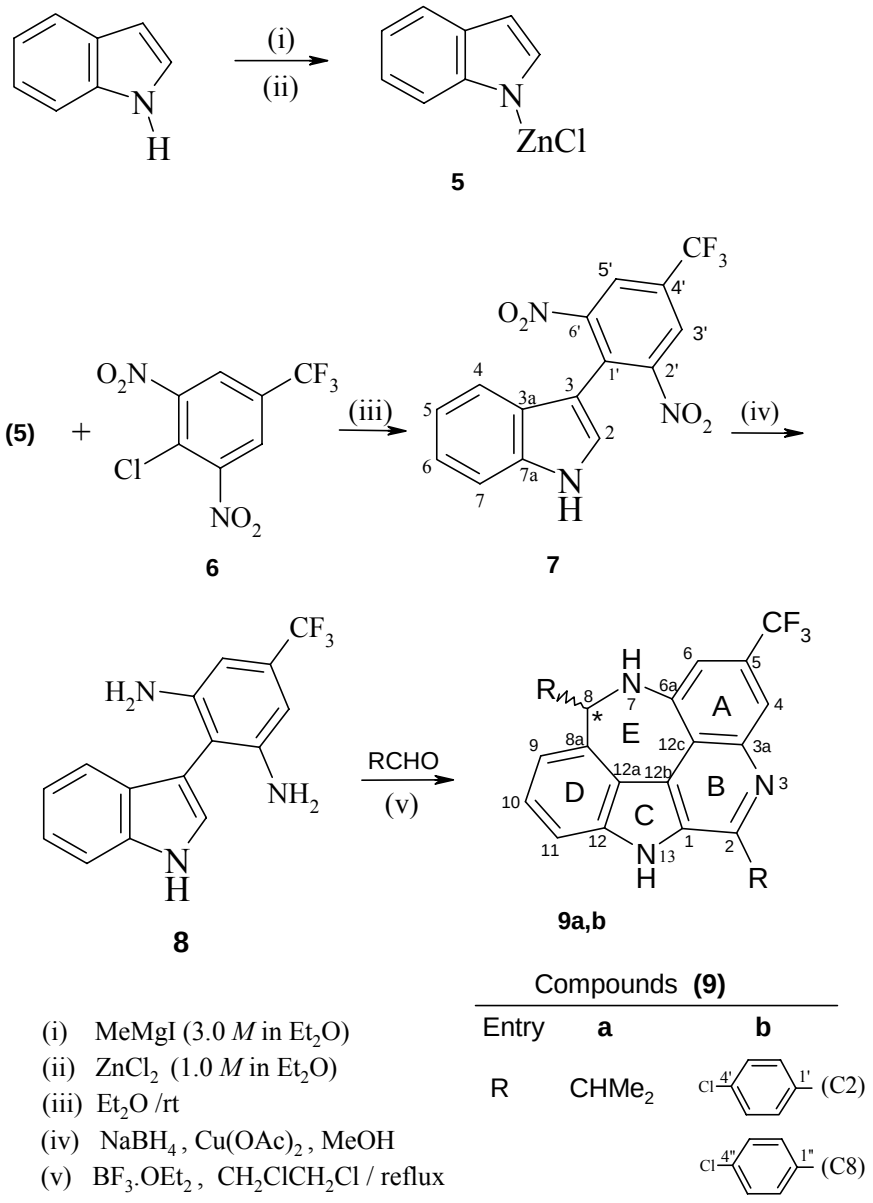
Accordingly, we envisage that Lewis acid-catalyzed condensation of a 3-[2'-(1',3'-diaminophenyl)]-indole (**8**) with aldehydes would bring about double cyclizations at the indolic C-2 and C-4 positions with ultimate formation of the corresponding azepine-fused indoloquinolines **(9a,b)**. This expectation is realized in this study, which deals with the synthesis and characterization of **9a,b** as outlined in Scheme 3. Our interest in this new pentacyclic ring system stems from the fact that it encompasses the following biologically active entities: (i) a dihydroazepino[5,4,3-*cd*]indole nucleus (rings C, D, E) present in the ergot alkaloid, claviciptic acid; [7] (ii) an indolo[2,3-*c*]quinoline nucleus (rings A, B, C, D) of which some synthetic derivatives exhibited antitumor potency; [8] (iii) a *β*-carboline unit (rings B, C, D) of natural occurrence in a wide variety of structures; [9] (iv) a dihydrobenzo[*b*]azepine (rings A, E), and (v) a hitherto unprecedented azepino[4,3,2-*de*]quinoline system (rings A, B, E).

RESULTS AND DISCUSSION

CHEMISTRY

In this study, 3-(2,6-dinitro-4-trifluoromethylphenyl)indole (**7**) was prepared *via* interaction of indolylzinc chloride (**5**)[10] with 2-chloro-1,3-dinitro-5-trifluoromethylbenzene (**6**). Copper(II) acetate/ sodium borohydride system[11] was employed for the reduction of **7** to afford the respective diamino derivative **(8)** (Scheme 1). Condensation of **8** with the appropriate aldehyde under Pictet-Spengler conditions, using boron triflouride etherate as a catalyst, delivered the respective target azepino-indoloquinolines **(9a,b)** namely, (±)-2,8-di*iso*propyl-5-trifluoromethyl-7,8-dihydro-1,12-iminobenzo[*c*]-pyrido[4,3,2-*ef*]benzazepine (**9a**), and its 2,8-di-(4-chlorophenyl) analog **(9b).** [12]

Scheme 3

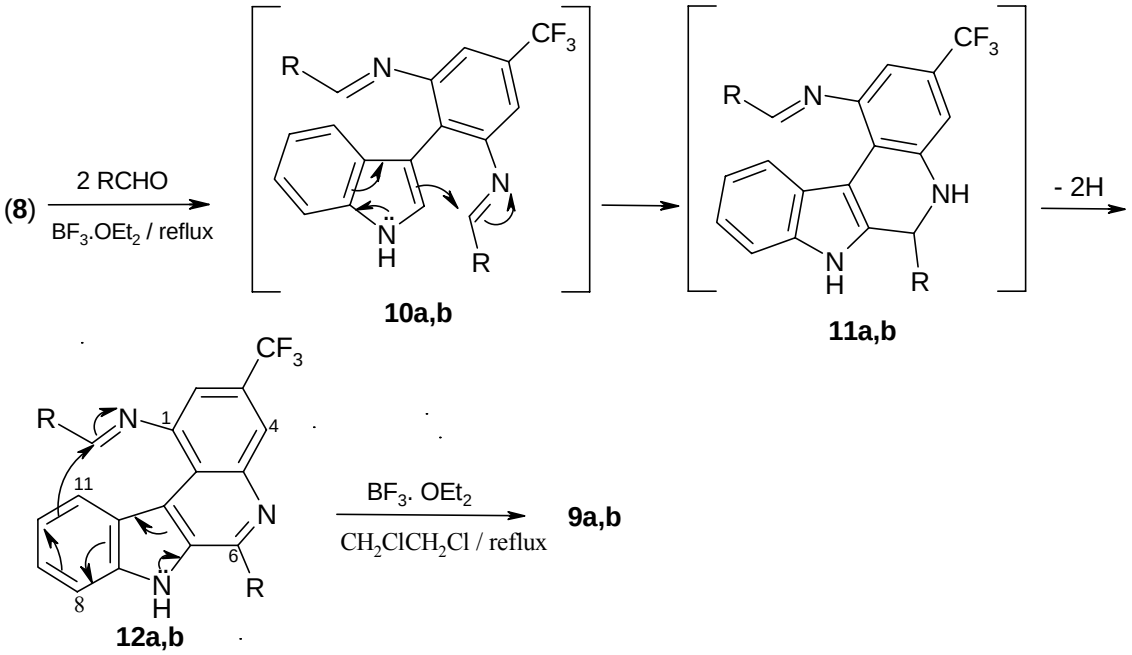


Compounds **(9)**

Entry	**a**	**b**
R	$CHMe_2$	(C2) (C8)

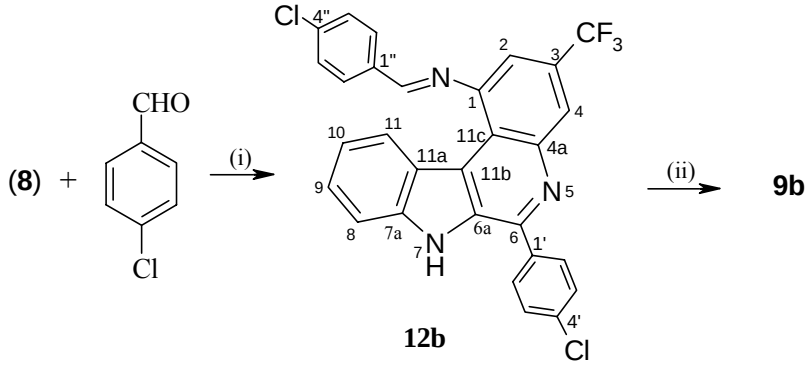
Apparently, the formation of **9a,b** proceeds *via* intermediate formation of the respective bis-imino derivatives **(10a,b)** (Scheme 4), which undergoes two consecutive intramolecular cyclizations at the indolic C-2 and C-4 positions. No attempt was, however, made to isolate the bis-imino substrates. We anticipate that cyclization occurs first at the more reactive pyrrolic C-2 locus of **10a,b**, leading to the formation of the corresponding dihydroindolo[2,3-*c*]quinoline intermediates **(11a,b)** which undergo aromatisation of the dihydropyridine nucleus through air oxidation under the reaction conditions, into the indolo[2,3-*c*]quinolines **(12a,b)** (Scheme 4). The latter intermediates **(12a,b)** undergo second cyclization involving the other *exo* - imine group and C-11 (recalled as the indolic C- 4 position) to deliver the final pentacyclic products **(9a,b)**.

Scheme 4



This assumption is substantiated by the actual isolation of the penultimate intermediate **(12b)** (Scheme 5), under neutral aprotic conditions. The latter tetracyclic compound (**12b**) was converted in a separate step, under acid- catalyzed Pictet-Spengler reaction conditions, into **9b** (Scheme 5). These experimental findings can be taken as supporting evidence for the timing of the two successive cyclizations of which annulation at C-2 precedes that occurring at the C- 4 locus.

Scheme 5



(i) CH_2ClCH_2Cl / reflux ; (ii) BF_3. OEt_2 , CH_2ClCH_2Cl / reflux

SPECTRAL DATA

The spectral (MS, NMR) and microanalytical data are compatible with the assigned structures (**7, 8, 9a,b** and **12b**), and are given in the experimental part. Thus, their MS spectra display the correct M^+ for which the measured HRMS data are in good agreement with the calculated values suggested by their molecular formulas. Assignments of the ^1H NMR signals to the different protons are straightforward, and ^{13}C-signal

assignments are based on DEPT and 2D (COSY, HMBC, HMQC) experiments, which showed correlations that helped in the full assignments of hydrogens and carbons. Thus, the HMBC spectra showed long-range correlations of H-8 with C-9, C-12a (**9a,b**) and with C-2'/C-6' (**9b**); likewise, both of H-4 and H-6 are correlated with C-12c. In the case of **9b**, H-2"/H-6" are correlated with C-2, while the *iso*propyl methine protons in **9a** are correlated with C-8a and C-1.

It is worth noting that the two doublets, belonging to H-2 and H-4 of the indole ring in the ^{1}H NMR of **8**, are absent from the ^{1}H NMR spectra of **9a,b**. The formation of the dihydroazepine ring (E) is manifested by the presence of the following diagnostic signals in the NMR spectra of **9a,b** : (i) The benzylic methine proton (H-8) in **9b** is appreciably deshielded and resonates at δ 6.0 as a doublet (due to coupling with the vicinal N_7-H) which collapses to a singlet upon addition of D_2O. In **9a**, the H-8 proton signal is centered at δ 4.23 as a doublet of doublet (a result of additional splitting by the vicinal methine proton of the *iso*propyl moiety) that changes to one doublet upon D_2O-addition; (ii) The exchangeable N_7-H proton is displayed as a doublet at δ 7.20 (**9a**) and δ 7.64 (**9b**) ppm; (iii) The benzylic tertiary sp^3-carbon (C-8) is deshielded (anchored to N_7) and resonates at δ 66.3 (**9a**), and δ 62.5 (**9b**) ppm.

Due to dissymmetry of the molecular structure of **9b**, the two *p*-chlorophenyls appended at C-2 and C-8 are chemically non-equivalent and give rise to signal doubling of their different ^{1}H- and ^{13}C- resonances. This trend of signal doubling is also observed in **9a** for the two non-equivalent isopropyl groups located at the C-2 and C-8 positions. The C-4, C-5 and C-6 signals are distinguishable as quartets by virtue of their characteristic couplings to fluorine nuclei of the nearby 5-CF_3 group. All in all, the spectral data of **9a,b** are in agreement with the dihydroazepine-fused indoloquinoline structure as determined by X-Ray crystal structure measurements (*vide infra*).

Collection of X-Ray Diffraction Data and the Structure Analysis of 9a and 9b

Yellow plate crystals of **9a** were grown by allowing a saturated solution of **9a** in 70 % aq. ethanol to evaporate slowly at room temperature over 3-4 days. Likewise, yellow rod crystals of **9b** were grown by allowing a clear solution of **9b** in 95 % ethanol to evaporate slowly at room temperature for 5-6 days.

For both compounds, data were collected with a Siemens SMART CCD diffractometer [Mo-Kα radiation (λ = 0.71073 Å), graphite monochromator] operating in the omega scan mode (0.3°). The data were reduced with the Siemens-Bruker program suite XSCANS, [13] and the structure was solved by the direct method using SHELXTL PLUS programs. [14] All non-hydrogen atoms were refined anisotropically by full-matrix, least-squares procedure based on F^2 using all unique data. The hydrogen atoms were located from the difference Fourier electron density synthesis and were then refined isotropically using a 'riding model'.

The derivative **(9a)** with *iso*propyl appendages has three independent molecules together with two water molecules in the asymmetric unit of an orthorhombic cell in the chiral space group $P2_12_12_1$; the absolute structure could not be determined reliably, and the crystallographic data are given in Table 1. The three molecules have comparable geometries of which only one is displayed in Figure 1; the essential bond distances and angles are given in Table 2. The predominant features are their almost planar shape with exception of the puckering of the heterocyclic seven-membered ring for which the respective atoms C8, C28 and C48, (one from each of the three molecules in the asymmetric unit) are the most deviating from planarity. In each molecule, these atoms C8A, C28A and C48A deviate from the mean plane of the molecule (apart from N7) by 0.23, 0.29 and 0.28 Å, respectively. The interplanar angles between these mean planes of the three molecules and the planes, formed by C8, C28 and C48 together with their two neighboring atoms, are 50.5, 51.8 and 47.7°; the torsion angles C6A-N7-C8-C8A, C26A-N27-C28-C28A and C46A-N47-C48-C48A are 81.3, 83.0 and -79.6°, respectively, thus demonstrating the similarities of the individual molecules. The three molecules form a trimeric motif linked *via* N–H···N hydrogen bonds (Figure 2), which is possible because the NH groups in the seven-membered heterocyles are made accessible by virtue of the influence of the neighboring axially positioned *iso*propyl groups (torsion angles C6A-N7-C8-C18, C26A-N27-C28-C38 and C46A-C47-C48-C58 are -43.9, 44.5 and 47.5°, respectively). The trimeric motifs are cross-linked by a complicated network of hydrogen bonds where two water molecules are involved as displayed in Figure 3. The most important hydrogen bonds are N7–H7···N47 (H···N 2.31 Å, N–H···N 179°, N···N 3.19 Å), N13–H13···N23 (H···N 2.34 Å, N–H···N 139°, N···N 3.06 Å), and N27···H47–N47 (H···N 2.43 Å, N–H···N 167°, N···N 3.30 Å). The hydrogen bonds involving the two water molecules are N33–H33···O2 (H···O 2.30 Å, N–H···O 156°, N···O 3.12 Å) and N53–H53···O1 (H···O 1.96 Å, N–H···N 164°, N···O 2.82 Å).

The molecular structure of **9b** incorporating *p*-chlorophenyl substituents (Figure 4, Table 1) is rather similar to that of **9a**. The central framework does not show any significant differences, whereas the main deviations exist at the external atoms (Table 3). Thus, the azepine ring of **9b** is more puckered, with C8 deviating by 0.31Å from the mean plane of the molecule (except for N7), and the interplanar angle to the plane formed by C8, N7 and C8A is 50.2°. The torsion angle C6A-N7-C8-C8a is 83.1°, similar to **9a**. A predominant difference is, however, the substitution at the seven-membered heterocycle. While the *iso*propyl substituent in **9a** is found in an axial position, the *p*-chlorophenyl substituent in **9b** occupies an equatorial position, the torsion angle C6A-N7-C8-C21 being 149.6°. This makes the hydrogen atom at N7 in **9b** less accessible for hydrogen bonding, as compared to **9a**. Instead, this N7 nitrogen atom is linked to the ethanol molecule, found in the asymmetric unit, forming a centrosymmetric dimer as shown in Figure 5 (N'7H···O1 2.39Å, O1···H7N'–N7' 114°, O1···N7' 2.88Å; N13H ···O1 1.97Å, O1···H13N–N13

Table 1. Summary of crystal data and structure refinement parameters for (±)-9a and (±)-9b

Empirical formula	$3\,(C_{23}H_{22}N_3F_3)\cdot 2(H_2O)$	$C_{29}H_{16}N_3Cl_2F_3\cdot C_2H_5OH$
Formula weight	409.45	580.42
Density (calculated) (g cm^{-3})	1.325	1.441
F(000)	2576	1192
Temperature (K)	173(2)	203(2)
Crystal size (mm)	0.48 x 0.18 x 0.15	0.21 x 0.11 x 0.05
Wavelength (Å)	0.71073	0.71073
Crystal system	orthorhombic	monoclinic
Space group	$P2_12_12_1$	$P2_1/n$
Unit cell dimensions		
a (Å)	13.139(3)	9.6230(11)
b (Å)	16.481(3)	11.6607(13)
c (Å)	28.444(6)	23.891(3)
β (°)		93.666(2)
Volume ($Å^3$)	6159(2)	2675.3(5)
Z	12	4
Theta range for data collection	1.89° to 23.99°	1.94° to 28.33°
Completeness to theta = 23.99°	99.7 %	99.6 %
Index ranges	$-15 \le h \le 15$, $-18 \le k \le 18$, $-32 \le l \le 32$	$-12 \le h \le 12$, $-15 \le k \le 15$, $-31 \le l \le 31$
Absorption coefficient (mm^{-1})	0.100	0.295
Max. / min. transmission	1.00 / 0.72	1.00 / 0.83
R(merg) before/after correction	0.1187 / 0.0690	0.0842 / 0.0517
Reflections collected	56141	10870
Independent reflections	9634 [R_{int} = 0.1718]	5737 [R_{int} = 0.0912]
Data / restraints / parameters	7386 / 0 / 820	2240 / 0 / 361
Goodness-of-fit on F^2	1.086	0.808
Weighting details	$w = 1/[\sigma^2(F_o^2)+(0.0715P)^2+7.7705\cdot P]$ where $P = (F_o^2+2F_c^2)/3$	$w = 1/[\sigma^2(F_o^2)+(0.055P)^2]$ where $P = (F_o^2+2F_c^2)/3$
Final *R* indices [$I > 2\sigma(I)$]	$R1$ = 0.0771, $wR2$ = 0.1778	$R1$ = 0.0555, $wR2$ = 0.1119
R indices (all data)	$R1$ = 0.1049, $wR2$ = 0.1999	$R1$ = 0.1363, $wR2$ = 0.1525
Absolute structure parameter	-1.1(14)	
Largest difference peak ($e\cdot Å^{-3}$)	0.601	0.440
Largest difference hole ($e\cdot Å^{-3}$)	-0.330	-0.340

Table 2. Selected bond lengths (Å) and angles (°) for (±)-9a.

N(7)-C(8)	1.466(7)	C(12C)-C(12B)-C(12A)	131.8(5)
C(6A)-N(7)	1.380(7)	C(8A)-C(12A)-C(12B)	132.4(6)
C(6A)-C(12C)	1.424(7)	C(12A)-C(8A)-C(8)	118.0(6)
C(12B)-C(12C)	1.400(7)	C(9)-C(8A)-C(8)	123.9(6)
C(12A)-C(12B)	1.431(8)	C(8A)-C(8)-C(18)	110.7(5)
C(8A)-C(12A)	1.369(9)	N(7)-C(6A)-C(6)	121.2(5)
C(8)-C(8A)	1.506(9)	C(12)-C(12A)-C(12B)	107.5(6)
C(12)-C(12A)	1.422(9)	N(13)-C(12)-C(12A)	106.0(6)
C(12)-N(13)	1.387(9)	C(11)-C(12)-N(13)	133.0(7)
C(1)-N(13)	1.366(7)	C(1)-N(13)-C(12)	110.6(5)
C(1)-C(12B)	1.381(8)	N(13)-C(1)-C(12B)	108.8(6)
C(1)-C(2)	1.388(9)	N(13)-C(1)-C(2)	131.5(6)
C(2)-N(3)	1.322(8)	C(1)-C(12B)-C(12A)	107.1(5)
N(3)-C(3A)	1.392(6)	C(1)-C(12B)-C(12C)	120.9(6)
C(3A)-C(12C)	1.408(8)	C(12B)-C(1)-C(2)	119.8(5)
		N(3)-C(2)-C(1)	121.4(5)
N(7)-C(8)-C(8A)	111.4(5)	C(2)-N(3)-C(3A)	119.0(5)
N(7)-C(8)-C(18)	112.7(5)	N(3)-C(3A)-C(12C)	122.8(5)
C(6A)-N(7)-C(8)	125.8(4)	N(3)-C(3A)-C(4)	118.2(5)
N(7)-C(6A)-C(12C)	120.6(4)	N(3)-C(2)-C(14)	119.1(7)
C(12B)-C(12C)-C(6A)	123.6(5)	C(1)-C(2)-C(14)	119.5(6)

156°, O1···N13 2.82Å). Comparison of the crystal structures **(9a)** and **(9b)** demonstrates the delicate interplay of solvent mediated hydrogen bonds, direct hydrogen bonds of the individual molecules and the importance of availability of hydrogen atoms for networking. Variation of solvents is expected to produce more pseudo polymorphs, a field which recently gained importance in pharmaceutical applications. However, this topic was not persecuted yet.

Supplementary Material

Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Center, CCDC No. 185223 for compound **(9a)**, and CCDC No. 185224 for compound **(9b)**. Copies of either information may be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge CB2 1 EZ, UK (Fax: +44-1223-336033; e-mail: (deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).

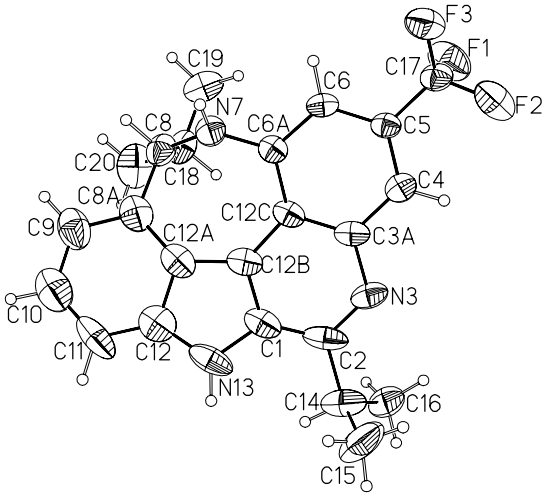


Figure 1. ORTEP plot (50%) of the molecular structure of **(±)-9a**.

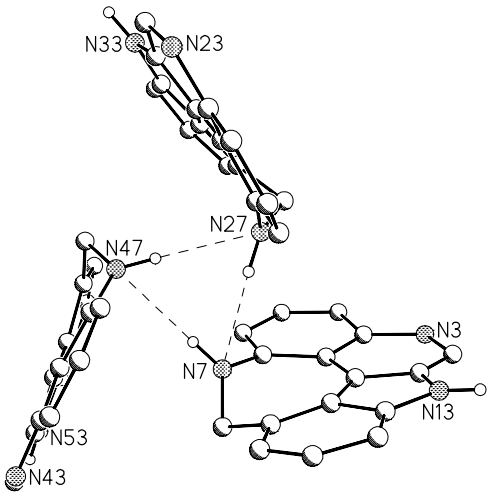


Figure 2. Drawing of the three independent molecules in the asymmetric unit of **(±)-9a** (non-relevant H-atoms and pendent groups are omitted).

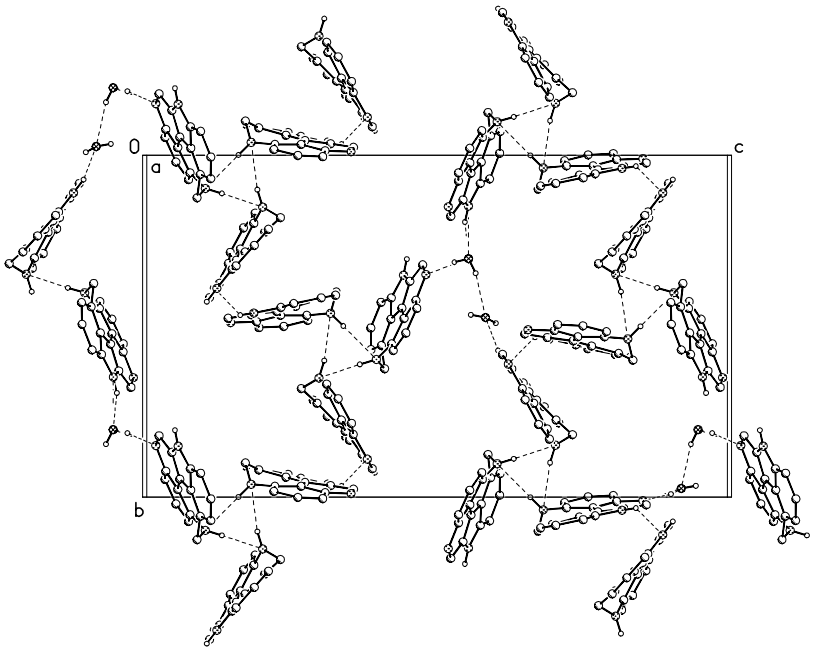


Figure 3. Drawing of the cell of the crystal structure of **(±)-9a** with the networking water molecules (non-relevant H-atoms and pendent groups are omitted).

Table 3. Selected bond lengths (Å) and angles (°) for (±)-9b.

N(7)-C(8)	1.497(4)	C(12C)-C(12B)-C(12A)	132.4(3)
C(6A)-N(7)	1.409(4)	C(8A)-C(12A)-C(12B)	132.0(3)
C(6A)-C(12C)	1.416(4)	C(12A)-C(8A)-C(8)	117.9(3)
C(12B)-C(12C)	1.413(4)	C(9)-C(8A)-C(8)	124.1(3)
C(12A)-C(12B)	1.433(4)	C(8A)-C(8)-C(21)	115.9(3)
C(8A)-C(12A)	1.395(4)	N(7)-C(6A)-C(6)	119.4(3)
C(8)-C(8A)	1.530(4)	C(12)-C(12A)-C(12B)	106.3(3)
C(12)-C(12A)	1.406(4)	N(13)-C(12)-C(12A)	108.9(3)
C(12)-N(13)	1.379(4)	C(11)-C(12)-N(13)	130.3(3)
C(1)-N(13)	1.379(4)	C(1)-N(13)-C(12)	108.9(2)
C(1)-C(12B)	1.400(4)	N(13)-C(1)-C(12B)	108.5(3)
C(1)-C(2)	1.413(4)	N(13)-C(1)-C(2)	131.2(3)
C(2)-N(3)	1.339(4)	C(1)-C(12B)-C(12A)	107.3(3)
N(3)-C(3A)	1.377(4)	C(1)-C(12B)-C(12C)	120.2(3)
C(3A)-C(12C)	1.420(4)	C(12B)-C(1)-C(2)	120.3(3)
		N(3)-C(2)-C(1)	120.2(3)
N(7)-C(8)-C(8A)	112.3(3)	C(2)-N(3)-C(3A)	120.1(3)
N(7)-C(8)-C(21)	106.8(3)	N(3)-C(3A)-C(12C)	123.1(3)
C(6A)-N(7)-C(8)	122.9(3)	N(3)-C(3A)-C(4)	117.4(3)
N(7)-C(6A)-C(12C)	121.3(3)	N(3)-C(2)-C(14)	114.8(3)
C(12B)-C(12C)-C(6A)	124.1(3)	C(1)-C(2)-C(14)	124.9(3)

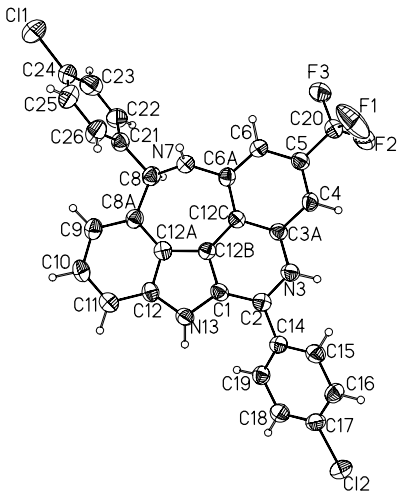


Figure 4. ORTEP plot (50%) of the molecular structure of **(±)-9b** (disorder of CF_3 group is omitted).

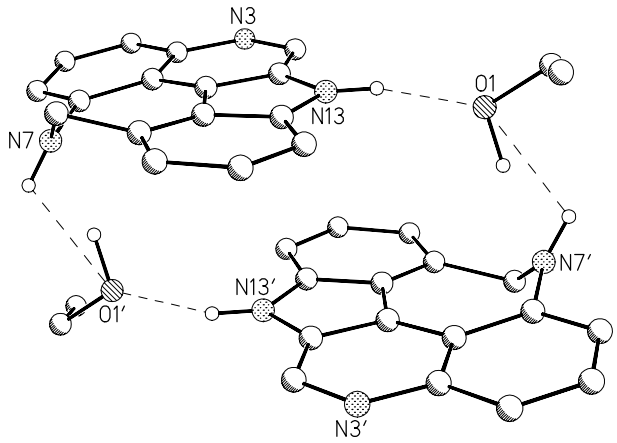


Figure 5. Ethanol hydrogen bonded dimer of **(±)-9b** (C-bonded H-atoms and pendent groups are omitted).

EXPERIMENTAL

2-Chloro-1,3-dinitro-5-trifluoromethylbenzene, indole and $NaBH_4$ were purchased from Acros. Methylmagnesium iodide (3.0 *M* in ether) and zinc chloride (1.0 *M* in ether) were purchased from Aldrich. Melting points (uncorrected) were determined on Gallenkamp melting point apparatus. NMR spectra were recorded on a Bruker DPX-300 spectrometer using TMS as internal reference. EIMS spectra and high resolution data were obtained using a Finnigan MAT TSQ-70 spectrometer at 70 eV ; ion source temperature = 200 ^{0}C. Microanalyses were performed at the Microanalytical Laboratory, Inorganic Chemistry Department, Tübingen University, Germany.

3-(2',6'-Dinitro-4'-trifluoromethylphenyl)indole (7)

To a solution of indole (2.3 g, 20 mmol) in dry ether (40 mL), an ethereal solution of methylmagnesium iodide (3.0 *M*, 8 mL) was added and stirred at rt for 20 min. An ethereal solution of zinc chloride (1.0 *M*, 24 mL) was then added and stirred at rt for 30 min. 2-Chloro-1,3- dinitro-5-trifluoromethylbenzene **6** (2.7 g, 10 mmol) was added to the reaction mixture , and stirring was continued at rt for 4 h. Water (100 mL) was then added, and stirred for 15 min. The ether layer was separated and the aqueous layer was extracted with ether (3 × 50 mL). The combined organic portions were dried over anhydrous sodium sulfate, and the solvent evaporated. The residual product was recrystallized from chloroform / petroleum ether (bp 40-60 °C) to afford a yellow solid. Yield of **7** = 1.9 g (54%), mp 139-141 °C. *Anal*. Calcd for $C_{15}H_8N_3O_4F_3$: C, 51.29; H, 2.30; N, 11.96; F, 16.23 . Found : C, 51.18; H, 2.21; N, 11.03; F, 15.88 . MS *m/z* (% rel. int.) : 351(M^+, 100), 322 (8), 305 (12), 276 (12), 248 (19), 222 (14), 182 (11), 179 (14), 149 (58), 120 (7), 119 (8); HRMS: Calcd for $C_{15}H_8N_3O_4F_3$: 351.04665. Found : 351.053506; ^{1}H NMR (300 MHz, $CDCl_3$) : δ 7.17 (dd, 1H, *J* = 7.4, 7.6 Hz, H-5), 7.27 (d, 1H, *J* = 7.6 Hz, H-4), 7.30 (dd, 1H, *J* = 8.0, 7.4 Hz, H-6), 7.39 (d, 1H, *J* = 2.8 Hz, H-2), 7.45 (d, 1H, *J* = 8.0 Hz, H-7), 8.23 (br s, 2H, H-3′/H-5′), 8.56 (br s, 1H, N_1-H); ^{13}C NMR (300 MHz, $CDCl_3$) : δ 104.3 (C-3), 111.9 (C-7), 118.0 (C-4), 121.6 (C-5), 123.5 (q, $^3J_{C-F}$ = 3.8 Hz, C-3′/ C-5′), 123.7 (C-6), 124.9 (C-2), 125.7 (C-3a), 127.4 (C-1′), 129.1 (q, $^1J_{C-F}$ = 256 Hz, $\underline{C}F_3$), 131.0 (q, $^2J_{C-F}$ = 36 Hz, C-4′), 135.7 (C-7a), 151.9 (C-2′/C-6′).

3-(2',6'-Diamino-4'-trifluoromethylphenyl)indole (8)

The following procedure is essentially similar to that reported [11] for nitro group reduction in related systems: to a stirred solution of 3-(2,6-dinitro-4-trifluoromethylphenyl)indole **(7)** (1.7 g, 5 mmol) in 60 mL of methanol and 20 mL of saturated solution of copper acetate, was added sodium borohydride (1.9 g, 40 mmol) portion wise at rt until the reduction was completed. This is followed by immediate addition of 100 mL of ether, and the mixture was washed with 10% sodium carbonate. The aqueous layer was further extracted with 40 mL of ether and the combined ether fractions were dried (anhydrous sodium sulfate),

filtered and the solvent was removed to yield 1.15 g of bright red solid which was recrystallized from dichloromethane-hexane. Yield of **8a** = 1.2 g (82 %), mp 162-164 °C. *Anal*. Calcd for $C_{15}H_{12}N_3F_3$: C, 61.85 ; H, 4.15; N, 14.43; F, 19.57 . Found : C, 62.10 ; H, 4.13; N, 14.50; F, 19.51. MS *m/z* (% rel. int.) : 291(M^+, 100), 274 (19), 273 (8), 272 (7), 247 (7), 221 (9), 205 (5), 153 (10), 146 (3), 138 (6), 111 (10); HRMS: Calcd for $C_{15}H_{12}N_3F_3$: 291.09833. Found : 291.09617; ^{1}H NMR (300 MHz, $CDCl_3$) : δ 3.67 (br s, 4H, $C_{2'}$-N*H*$_2$ / $C_{6'}$-N*H*$_2$), 6.46 (br s, 2H, H-3′/ H-5′), 7.15 (dd, 1H, *J* = 7.4, 8.0 Hz, H-5), 7.28 (dd, 1H, *J* = 7.4, 8.2 Hz, H-6), 7.30 (d, 1H, *J* = 2.0 Hz, H-2), 7.44 (d, 1H, *J* = 8.0 Hz, H-4), 7.48 (d, 1H, *J* = 8.2 Hz, H-7), 8.47 (br s, 1H, N_1-*H*); ^{13}C NMR (75 MHz, $CDCl_3$) : δ 101.7 (q, $^3J_{C\text{-}F}$ = 3.8 Hz, C-3′/ C-5′), 108.1 (C-1′), 108.4 (C-3), 111.6 (C-7), 119.9 (C-4), 120.4 (C-5), 123.0 (C-6), 124.3 (C-2), 124.4 (q, $^1J_{C\text{-}F}$ = 271 Hz, $\underline{C}F_3$), 126.0 (C-3a), 131.1 (q, $^2J_{C\text{-}F}$ = 32 Hz, C-4′), 136.7 (C-7a), 146.9 (C-2′/ C-6′).

1-(4''-Chlorobenzylidinimino)-6-(4'-chlorophenyl)-7H-3-trifluoromethylindolo[2,3-c]quinoline (12b)

A solution of **8** (1.46 g, 5 mmol), and 4-chlorobenzaldehyde (1.45 g, 11 mmol) in 50 ml of 1,2-dichloroethane was refluxed (oil bath, 90 °C) for 6 h. The solvent was evaporated, the residue was soaked successively with 5% NaOH solution, and water (2 × 20 mL), collected, dried, and recrystallized from CH_2Cl_2 / petroleum ether as bright yellow solid. Yield of **12b** = 2.47 g (93 %), mp 257-259 °C. *Anal*. Calcd for $C_{29}H_{16}N_3Cl_2F_3$: C, 65.18 ; H, 3.02; N, 7.86; Cl, 13.27 . Found : C, 65.04 ; H, 3.07; N, 7.95; Cl, 13.19. MS *m/z* (% rel. int.) : 533 (M^+, 39), 422 (100), 360 (6), 268 (10), 267 (15), 249 (8), 211 (35), 188 (42), 146 (9); HRMS: Calcd for $C_{29}H_{16}N_3Cl_2F_3$: 533.067307. Found : 533.063713; ^{1}H NMR (300 MHz, DMSO-d_6) : δ 7.05 (dd, 1H, *J* = 7.4, 8.5 Hz, H-10), 7.48 (dd, 1H, *J* = 7.4, 8.2 Hz, H-9), 7.58 (br s, 1H, H-4), 7.71 (d, 1H, *J* = 8.5 Hz, H-11), 7.76 (d, 4H, *J* = 8.3 Hz, H-3′/ H-5′ and H-3′′/ H-5′′), 8.09 (d, 2H, *J* = 8.3 Hz, H-2′′/ H-6′′), 8.18 (d, 2H, *J* = 8.3 Hz, H-2′/ H-6′), 8.38 (br s, 1H, H-2), 9.24 (d, 1H, *J* = 8.2 Hz, H-8), 12.20 (br s, 1H, N_7-*H*); ^{13}C NMR (75 MHz, DMSO-d_6) : δ 111.8 (q, $^3J_{C\text{-}F}$ = 3.6 Hz, C-4), 113.2 (C-8), 120.2 (C-11), 121.1 (C-11b), 122.3 (C-6a), 122.5 (C-11c), 125.1 (q, $^3J_{C\text{-}F}$ = 3.6 Hz, C-2), 126.2 (q, $^2J_{C\text{-}F}$ = 38 Hz, C-3), 126.6 (q, $^1J_{C\text{-}F}$ = 270 Hz, $\underline{C}F_3$), 127.4 (C-10), 127.6 (C-9), 129.4 (C-3′′/ C-5′′), 129.7 (C-3′/ C-5′), 131.4 (C-2′′/ C-6′′), 131.7 (C-2′/ C-6′), 132.5 (C-7a), 134.8 (C-4′′), 135.1 (C-4′), 136.5 (C-1′′), 137.4 (C-1′), 140.9 (C-11a), 143.0 (C-4a), 148.2 (C-6), 150.5 (C-1), 162.0 (exocyclic $\underline{C}$=N-C_1).

(±)-2,8-Diisopropyl-5-trifluoromethyl-7,8-dihydro-1,12-iminobenzo[c]pyrido[4,3,2-ef][1]benzazepines (9a)

A mixture of **8** (1.46 g, 5 mmol) and isobutyraldehyde (0.8 g, 11 mmol) dissolved in 50 mL of 1,2-dichloroethane and few drops of glacial acetic acid, was stirred at rt for 1 h. $BF_3.OEt_2$ (3 mL) was added, and the mixture was refluxed (oil bath, 80 °C) for 2 h. The solvent was evaporated and the residue was

soaked successively with 5% NaOH solution and water (2 × 20 mL). The resulting solid product was collected, dried, and purified using silica gel column chromatography, eluting with CH_2Cl_2. Yield of **9a** = 1.43 g (76 %), mp 141-144 °C. *Anal.* Calcd for $C_{23}H_{22}N_3F_3$: C, 69.51 ; H, 5.58 ; N, 10.57. Found : C, 69.38 ; H, 5.64 ; N, 10.56. MS *m/z* (% rel. int.) : 397(M^+, 7), 354 (100), 338 (16), 304 (23), 289 (3), 234 (2), 205 (3), 177 (3), 170 (8), 149 (38), 137 (4), 111 (6); HRMS: Calcd for $C_{23}H_{22}N_3F_3$: 397.17658. Found : 397.17806; ^{1}H NMR (300 MHz, DMSO-d_6) : δ 0.47, 1.03 (2d, 3H/3H, *J* = 6.3, 6.5 Hz, C_8-CH(C<u>*H*</u>$_3$)$_2$), 1.47 (d, 6H, *J* = 6.5 Hz, C_2-CH(C<u>*H*</u>$_3$)$_2$), 1.56 (m, 1H, C_8-C<u>*H*</u>Me_2), 3.81 (m, 1H, C_2-C<u>*H*</u>Me_2), 4.23 (dd, 1H, *J* = 5.8, 7.8 Hz, H-8), 7.09 (d, 1H, *J* = 6.9 Hz, H-9), 7.20 (d, 1H, *J* = 5.8 Hz, N_7-<u>*H*</u>), 7.26 (br s, 1H, H-4), 7.49 (dd, 1H, *J* = 6.9, 8.0 Hz, H-10), 7.59 (d, 1H, *J* = 8.0 Hz, H-11), 7.75 (br s, 1H, H-6), 12.19 (br s, 1H, N_{13}-<u>*H*</u>); ^{13}C NMR (75 MHz, DMSO-d_6) : δ 14.4, 20.6 (C_8-CH(<u>*C*</u>H$_3$)$_2$), 21.1, 21.3 (C_2-CH(<u>*C*</u>H$_3$)$_2$), 31.7 (C_8-<u>*C*</u>HMe_2), 33.4 (C_2-<u>*C*</u>HMe_2), 66.3 (C-8), 106.9 (q, $^3J_{C\text{-}F}$ = 3.0 Hz, C-4), 110.5 (C-11), 115.5 (q, $^3J_{C\text{-}F}$ = 3.8 Hz, C-6), 117.8 (C-9), 118.3 (C-12b), 120.4 (C-1), 120.6 (C-12c), 124.9 (q, $^1J_{C\text{-}F}$ = 271 Hz, <u>*C*</u>F$_3$), 126.1 (q, $^2J_{C\text{-}F}$ = 32 Hz, C-5), 126.5 (C-10), 129.5 (C-12), 141.6 (C-3a), 146.0 (C-2), 155.2 (C-6a).

(±)-2,8-Di-(4-chlorophenyl)-5-trifluoromethyl-7,8-dihydro-1,12-iminobenzo[c]pyrido[4,3,2-ef][1]benz-azepines (9b)

Method A. This compound was prepared from **8** (1.46 g, 5 mmol), and 4-chlorobenzaldehyde (1.54 g, 11 mmol) following the same procedure and experimental conditions noted above for **9a**. Yield of **9b** = 1.63 g (61 %), mp 251-253 °C.

Method B. This compound was also prepared from **12b** (2.12 g, 4 mmol), dissolved in 40 mL of 1,2-dichloroethane, and 3 mL of $BF_3.OEt_2$. The reaction mixture was refluxed (oil bath, 80 °C) for 2 h. The solvent was evaporated and the residue was soaked successively with 5% NaOH solution (20 mL), and water (2 × 20 mL). The resultant solid product was collected, dried, and purified using silica gel column chromatography, eluting with CH_2Cl_2. Yield of **9b** = 1.47 g (69 %), mp 251-253 °C, undepressed upon admixture with an authentic sample of **9b**, prepared by method A above. *Anal*. Calcd for $C_{29}H_{16}N_3Cl_2F_3$: C, 65.18; H, 3.02; N, 7.86; Cl , 13.27 . Found : C, 65.13; H, 3.08; N, 7.75; Cl , 13.21. MS *m/z* (% rel. int.) : 533(M^+ , 48), 514 (3), 496 (3), 424 (34), 422 (100), 386 (7), 352 (3), 310 (5), 267 (21), 258 (18), 240 (12), 210 (29), 194 (27), 158 (10), 144 (4), 111 (3); HRMS: Calcd for $C_{29}H_{16}N_3Cl_2F_3$: 533.06622. Found : 533.06734; ^{1}H NMR (300 MHz, DMSO-d_6) : δ 6.05 (d, 1H, *J* = 5.3 Hz, H-8), 6.90 (d, 2H, *J* = 8.4 Hz, H-3′′/ H-5′′), 7.16 (d, 2H, *J* = 8.4 Hz, H-2′′/ H-6′′), 7.18 (d, 1H, *J* = 7.3 Hz, H-9); 7.29 (br s, 1H, H-4), 7.58 (dd, 1H, *J* = 7.3, 8.2 Hz, H-10), 7.64 (d, 1H, *J* = 5.3 Hz, N_7-<u>*H*</u>), 7.71 (d, 2H, *J* = 8.4 Hz, H-3′/ H-5′), 7.73 (d, 1H, *J* = 8.2 Hz, H-11), 7.85 (br s, 1H, H-6), 8.17 (d, 2H, *J* = 8.4 Hz, H-2′/ H-

6′), 12.23 (br s, 1H, N_{13}-*H*); ^{13}C NMR (75 MHz, DMSO-d_6) : δ 62.5 (C-8), 108.6 (q, $^{3}J_{C\text{-}F}$ = 3.6 Hz, C-4), 112.1 (C-11), 117.1 (q, $^{3}J_{C\text{-}F}$ = 3.6 Hz, C-6), 118.7 (C-9), 118.9 (C-12b), 121.5 (C-1), 122.8 (C-12c), 125.2 (q, $^{1}J_{C\text{-}F}$ = 271 Hz, *C*F_3), 127.4 (q, $^{2}J_{C\text{-}F}$ = 32 Hz, C-5), 128.3 (C-10), 128.8 (C-3′′/ C-5′′), 129.4 (C-3′/ C-5′), 129.5 (C-2′′/ C-6′′), 129.8 (C-12), 131.2 (C-2′/ C-6′), 132.0 (C-1′′), 135.0 (C-1′), 136.8 (C-4′′), 137.1 (C-4′), 140.3 (C-8a), 142.3 (C-12a), 142.9 (C-3a), 146.1 (C-2), 146.3 (C-6a).

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REFERENCES AND NOTES

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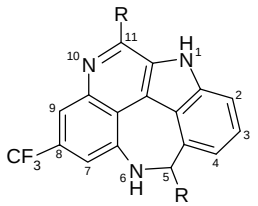
1. (a) K. Staurt and R. Woo-Ming, *Heterocycles*, 1975, **3**, 223. (b) M. Julia, J. Bagot, and O. Siffert, *Bull. Soc. Chim Fr.*, 1973, 1424. (c) J. Bergman, *Acta Chem. Scand.*, 1971, **25**, 3296. (d) J. Degraw, J. G. Kennedy, and W. A. Skinner, *J. Med. Chem.*, 1967, **10**, 127.
2. (a) J. Sandrin, D. Soerens, P. Mokry, and J. M. Cook, *Heterocycles*, 1977, **6**, 1133. (b) D. Soerens, J. Sandrin, F. Ungemach, P. Mokry, G. S. Wu, E. Yamanaka, L. Hutchins, M. DiPierro, and J. M. Cook, *J. Org. Chem.*, 1979, **44**, 535.
3. (a) L. Deng, K. M. Czerwinski, and J. M. Cook, *Tetrahedron Lett.*, 1991, **32**, 175. (b) K. M. Czerwinski, L. Deng, and J. M. Cook, *Tetrahedron Lett.*, 1992, **33**, 4721.
4. E. D. Cox and J. M. Cook, *Chem. Rev.*, 1995, **95**, 1797.
5. (a) P. D. Bailey, S. P. Hollinshead, N. R. McLay, K. Morgan, S. J. Palmer, S. N. Prince, C. D. Reynolds, and S. D. Wood, *J. Chem. Soc.*, *Perkin Trans. I*, 1993, 431. (b) G. Casnati, A. Dossena, and A. Pochini, *Tetrahedron Lett.*, 1972, 5277. (c) A. H. Jackson, B. J. Naidoo, and P. Smith, *Tetrahedron*, 1968, **24**, 6119.
6. S-I. Nakatsuka, H. Miyazaki, and T. Goto, *Tetrahedron Lett.*, 1986, **27**, 4757.
7. (a) G. S. King, P. G. Mantle, C. A. Szczyrbak, and E. S. Waight, *Tetrahedron Lett.*, 1973, 215. (b) G. S. King, E. S. Waight, P. G. Mantle, and C. A. Szczyrbak, *J. Chem. Soc., Perkin Trans. I*, 1977, 2099. (c) D. A. Boyles and D. E. Nichols, *J. Org. Chem.*, 1988, **53**, 5128. (d) M. Iwao and F. Ishibashi, *Tetrahedron*, 1997, **53**, 51. (e) Y. Yokoyama, T. Matsumoto, and Y. Murakami, *J. Org. Chem.*, 1995, **60**, 1486. (f) M. Somei, S. Hamamoto, K. Nakagawa, F. Yamada, and T. Ohta, *Heterocycles*, 1994, **37**,

719. (g) L. Novák, M. Hanania, P. Kovács, J. Rohály, P. Kolonits, and C. Szántay, *Heterocycles*, 1997, **45**, 2331.

8. (a) R. I. Fryer, R. Y. F. Ning, L. H. Sternbach, and A. Walser (Hofmann-La Roche, Inc.), *Swiss Patent* **CH 602 728** (1978), 6 pp (*Chem. Abstr*., 1978, **89**, 146890z). (b) R. I. Fryer, R. Y. F. Ning, L. H. Sternbach, and A. Walser, *US Patent* **4, 014, 883** (1977), 26 pp (*Chem. Abstr*., 1977, **87**, 39450t). (c) N. Strojny , L. D'Arconte, and J. A. F. de Silva, *J. Chromatogr.*, 1981, **223**, 111. (d) E. Grunberg, M. J. Kramer, M. Buch, and P. W. Trown, *Chemotherapy*, 1978, **24**, 77. (e) A. Walser, G. Silverman, T. Flynn, and R. I. Fryer, *J. Heterocycl. Chem.*, 1975, **12**, 351.
9. (a) R. A. Abramouvitch and I. D. Spenser, "*Advanced Heterocyclic Chemistry* : The *β*-Carbolines" , Vol. **3**, ed. by A. R. Katritzky, A. J. Boulton, and J. M. Lagowski, Academic Press, New York, 1964, pp. 79-207. (b) A. Brossi, " The alkaloids ", Vol. **XXII**, Academic Press, New York, 1983, Chapters 1 and 4. (c) B. J. Baker, "Alkaloids : Chemical and Biological Perspectives", Vol. **10**, ed. by W. Pelletier, Pergmon Press, Oxford, 1996, pp. 357-407.
10. For the preparation of *N*-indolylmetal salts and their utilization in the synthesis of 3-(heteroaryl)-indoles, see : (a) R. A. Heacock and S. Kăspárek, "*Advances in Heterocyclic Chemistry* : The Indole Grignard Reagents", Vol. **10**, ed. by A. R. Katritzky and A. J. Boulton , Academic Press, New York, 1969, pp. 43-112. (b) J. Bergman and L. Venemalm, *Tetrahedron*, 1990, **46**, 6061. (c) W. A. Ayer, P. A. Craw, Y-T. Ma, and S. Mialo, *Tetrahedron,* 1992, **48**, 2919. (d) K. A. Abu Safieh, M. M. El-Abadelah, S. S. Sabri, M. H. Abu Zarga, W. Voelter, and C. M.-Mössmer, *J. Heterocycl. Chem*., 2001, **38**, 623, and references cited therein.
11. J. A. Cowan, *Tetrahedron Lett.*, 1986, **27**, 1205. See also: H. V. Patel , K. A. Vyas, S. P. Pandey, and P. S. Fernandes, *Organic Preparations and Procedures Int.*, 1995, **27**, 81.
12. The pentacyclic skeleton of **9a,b** is also named, by the hetero-substitution (replacement) method, as follows: 5,6-dihydro-1*H*-1,6,10-triazabenzo[*ij*]naphtha[2,1,8-*cde*]azulene.
13. R. H. Blessing, *Acta Crystallogr*., 1995, **A51**, 33.
14. G. M. Sheldrick, SHELXTL PLUS System of computer programs for the determination of crystal structure from the X-Ray diffraction data, Vers.5.10.DOS/WIN 95/NT.



9a,b