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Synthesis of Tröger's Base Analogs Derived from 3-Aminoacridine and 10-Aminobenzo[b][1,7]Phenanthroline

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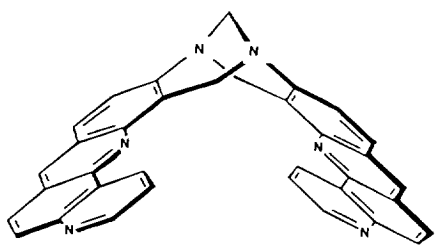
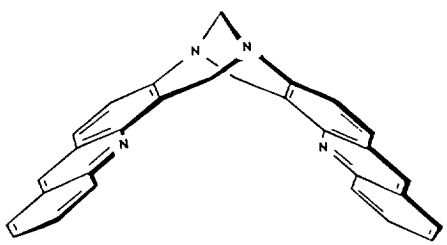
Abstract: The heterocyclic aromatic amines 10-aminobenzo[b][1,7]phenanthroline **1** and 3-aminoacridine **2** react regioselectively with formaldehyde in acidic medium to yield the Tröger's base analogs **7** and **8**.

Tröger's bases have been recently described as "fascinating molecules"[1] due to the particular features present in their structure in which the chiral 1,5-diazocine bridge locks two aromatic rings in perpendicular planes. Renewal interest for this class of compounds has recently emerged in connection with molecular recognition problems and supramolecular chemistry[2]. Tröger's bases result from selective ortho electrophilic substitution in aromatic amines by formaldehyde, which explains that most reported Tröger's bases derive from symetrical 4-substituted anilines and not from π-electron deficient heterocyclic amines[3]. In the course of a program devoted to the study of acridine derivatives we observed an increased rate of H/D exchange in the 4 and 5 positions of 3,6-diaminoacridine. We took advantage of this property to build up a new ring upon the acridine nucleus and prepare new DNA-interacting molecules of pharmaceutical interest[4]. We made further use of this reactivity and selectivity to prepare Tröger's bases derived from typical DNA-binders such as 3-aminoacridine



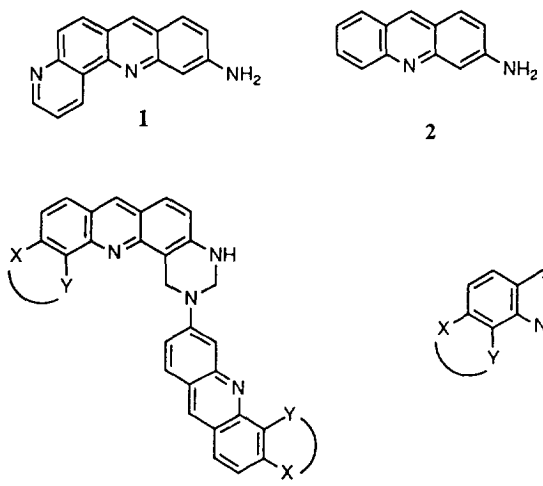
7



8

derivatives[5]. Such molecules are of great promise as DNA probes[6] due to their different possible modes of interaction with DNA and to their chiral properties. We report here the preparation of the new Tröger's base analogs **7** and **8**.

Reaction of 11-aminobenzo[b][1,7]phenanthroline **1** or 3-aminoacridine **2** with formaldehyde in acidic conditions gave three types of products : the "dimeric" compounds **3** and **4**, the dihydro [3,1] oxazines **5** et **6** and the Tröger's base derivatives **7** and **8** respectively.



1 **2**

3 X Y : -N=CH-CH=CH- **5**

4 X = Y = H **6**

All compounds **3-8** were identified by their analytical and spectroscopic data[7]. Interestingly the ^1H NMR spectra exhibited quite specific features characteristic of each type of structure. The "dimeric" compounds **3** and **4** were characterized by the presence of two sets of signals corresponding to the two differently substituted aromatic nuclei. The spectra of the dihydrooxazine derivatives **5** and **6** showed, in addition to the aromatic signals, two sharp singlets corresponding to the two methylenes of the dihydrooxazine ring (at 5.58 and 4.88 ppm for **5** and 5.45 and 4.90 ppm for **6**) and a large NH signal at 4.75 and 4.50 ppm respectively for **5** and **6**. Finally, the Tröger's base spectra were distinguished by the presence of a singlet integrating for two protons and corresponding to the methylene of the bridge (4.63 ppm for **7** and 4.57 ppm for **8**). The two benzylic type methylene protons appeared as two doublets (AB type signals)[8]. The structure of **8** was further confirmed by x-ray analysis.

As shown in the table, the two heterocycles **1** and **2** react quite similarly. For both compounds the relative yields of the different compounds were highly dependent upon the nature and concentration of the acid used. In 6N hydrochloric acid, no Tröger's base derivative was formed. The "dimeric" compounds **3** and **4** and the dihydrooxazines **5** and **6** were isolated in relatively low yields. In more acidic conditions (12N hydrochloric acid), the "dimeric" structures were not observed. The Tröger's bases **7** and **8** were obtained in 52 and 70 % yields respectively, the dihydrooxazines being formed as minor products. Using trifluoroacetic acid increased dramatically the selectivity of the reaction. The Tröger's bases were formed almost exclusively in more than 90 % yield (as determined by hplc analysis) ; the dihydrooxazines were the only by-products.

Starting compounds	Conditions[a]	**3** or **4** (%)	**5** or **6** (%)	**7** or **8** (%)
1	6N HCl	32	15	0
2	6N HCl	35	15	0
1	12N HCl	0	42[b]	52[b]
2	12N HCl	0	30	70
1	TFA	0	5-10[b]	90[b]
2	TFA	0	5-10[b]	90[b]

a : In 6N and 12N HCl, 6 equivalents of paraformaldehyde were used, in TFA, 1.5 equivalents of formaldehyde were used. The reactions were performed at room temperature.

b : yields determined by hplc analysis

Formation of the "dimeric" structures **3** and **4** and of the Tröger's bases **7** and **8** are closely related. "Dimeric" compounds such **3** and **4** are intermediates in the synthesis of the Tröger's bases[9]. And indeed, by adding formaldehyde to compound **4** dissolved in 12N HCl the corresponding Tröger's base **8** was formed quantitatively. At the opposite, formation of the dihydrooxazines and of the Tröger's bases appeared to be competitive. The yield in Tröger's base was optimized by using the exact required stoechiometry (1.5 equivalents of paraformaldehyde) and trifluoroacetic acid as solvent[10].

As previously observed in the 3,6-diaminoacridine series, the electrophilic reaction is totally regioselective. No reaction product corresponding to the attack at the other ortho position was detected.

Efforts are now devoted to resolve the racemic Tröger's bases and to study their interaction with DNA.

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7. Compound **3** : mp : 275°C (dec.) ; ^{1}H nmr (400 MHz, DMSOd$_6$) δ (ppm) = 9.74 (1H, ddd, J = 8.1 Hz, J = 1.8 Hz and J = 0.7 Hz) ; 9.37 (1H, ddd, J = 8.2 Hz, J = 1.8 Hz and J = 0.7 Hz) ; 9.00 (1H, dd, J = 4.4 Hz and J = 1.8 Hz) ; 8.90 (1H, dd, J = 4.4 Hz and J = 1.8 Hz) ; 8.77 (1H, s) ; 8.71 (1H, s) ; 8.04 (1H, d, J = 9.2 Hz) ; 8.03 (1H, d, J = 9.3 Hz) ; 8.02 (1H, d, J = 9.2 Hz) ; 7.82 (1H, dd, J = 9.3 Hz and

J = 2.5 Hz) ; 7.78 (1H, d, J = 9.0 Hz) ; 7.77 (1H, dd, J = 8.1 Hz and J = 4.4 Hz) ; 7.74 (1H, dd, J = 9.2 Hz and J = 0.7 Hz) ; 7.71 (1H, dd, J = 9.2 Hz and J = 0.7 Hz) ; 7.61 (1H, d, J = 2.5 Hz) ; 7.58 (1H, dd, J = 8.2 Hz and J = 4.4 Hz) ; 7.21 (1H, t, NH) ; 7.08 (1H, d, J = 9.0 Hz) ; 5.46 (2H, s) ; 5.12 (2H, d). ms (CI, NH_3 + isobutane) m/z = 515 (100, $(M+1)^+$) ; 428 (4) ; 396 (12) ; 382 (20) ; 350 (5) ; 331 (9). UV (Ethanol) : λ_{max} (ε) : 321 (64100) ; 311 (61300) ; 275 (94000) ; 242 (64600) nm. Anal. Calcd. for $C_{34}H_{22}N_6$, 0.5 H_2O : C, 77.99 ; H, 4.43 ; N, 16.05. Found : C, 78.24 ; H, 4.87 ; N, 15.73.

Compound **4** : mp : 175-178°C. ^1H nmr (300 MHz, $DMSOd_6$) δ (ppm) = 8.85 (1H, s,) ; 8.76 (1H, s) ; 8.10 (1H, d, J = 8.5 Hz) ; 8.04-8.00 (2H, m) ; 7.92 (1H, d, J = 8.5 Hz) ; 7.79-7.68 (5H, m) ; 7.48-7.41 (2H, m) ; 7.36 (1H, s) ; 7.25 (1H, s, N-H) ; 7.03 (1H, d, J = 9 Hz) ; 5.27 (2H, s, Ar-CH_2-N) ; 5.11 (2H, s, N-CH_2-N). ms (CI, NH_3 + isobutane) m/z = 413 (100, $(M+1)^+$). UV (Ethanol) : λ_{max} (ε) : 417 (11000), 356 (1200), 340 (9100), 278 (63000), 271 (62000), 241 (62400) nm.

Compound **5** : mp :223-224°C. ^1H nmr (300 MHz, $CDCl_3$) : δ (ppm) = 9.58 (1H, dd, J = 8.2 Hz and J = 1.8 Hz) ; 8.95 (1H, dd, J = 4.5 Hz and J = 1.8 Hz) ; 8.47 (1H, s) ; 7.89 (1H, d, J = 9.2 Hz) ; 7.82 (1H, d, J = 9.0 Hz) ; 7.73 (1H, d, J = 9.2 Hz) ; 7.56 (1H, dd, J = 8.2 Hz and J = 4.5 Hz) ; 7.09 (1H, d, J = 9.0 Hz) ; 5.58 (2H, s) ; 4.88 (2H, d, J = 5.2 Hz) ; 4.75 (1H, m, NH). ms (EI) : m/z = 287 (41, $M^{+\bullet}$) ; 258 (38) ; 230 (100). Anal. Calcd. for $C_{18}H_{13}N_3O$: C, 75.24 ; H, 4.56 ; N, 14.62. Found : C, 74.95 ; H, 4.49 ; N, 14.10.

Compound **6** : mp : 180°C ; ^1H nmr (200 MHz, $CDCl_3$) : δ (ppm) = 8.65 (1H, s) ; 8.05 (1H, dd, J = 8.6 Hz and J = 2 Hz) ; 7.85 (1H, d, J = 8.4 Hz) ; 7.65 (1H, d, J = 9.0 Hz) ; 7.6 (1H, dd, J = 8.6 Hz et J = 6.6 Hz) ; 7.4 (1H, ddd, J = 8.4 Hz, J = 6.6 Hz et J = 2.0 Hz) ; 6.9 (1H, d, J = 9.0 Hz) ; 5.45 (2H, s, Ar-CH_2-O) ; 4.9 (2H, s, O-CH_2-N) ; 4.5 (1H, s, NH) ; ms (FAB(+), NBA) : m/z : 236 (100, M^+), 207 (60), 179 (66). UV (Ethanol) : λ_{max} (ε) : 418 (5300), 354 (6100), 273 (52200), 240 (32800) nm. Anal. Calc. for $C_{15}H_{12}N_2O$: C, 76.25 ; H, 12.00 ; N, 11.86. Found : C, 76.1 ; H, 5.07 ; N, 11.6.

Compound **7** : mp : 360°C ; ^1H nmr (200 MHz, $CDCl_3$) δ(ppm) = 9.65 (2H, dd, J = 8.1 Hz and J = 1.7 Hz, H-1) ; 8.97 (2H, dd, J = 4.42 Hz et J = 1.7 Hz, H-3) ; 8.44 (2H, s, H-7) ; 7.84 (2H, s, H-5 and H-6) ; 7.7 (2H, d, J = 8.9 Hz, H-8) ; 7.6 (2H, dd, J = 8 Hz et J = 4.4 Hz, H-2) ; 7.5 (2H, d, J = 9 Hz, H-9) ; 5.3 (4H, q, Ar-CH_2-N) ; 4.63 (2H, s, N-CH_2-N). ms (FAB(+), NBA) ; m = 526 ; m/z = 527 $(M+1)^+$. UV (Ethanol) : λ_{max} (ε) : 309.6 (61631) ; 260.2 (63947) ; 208.8 (127947) nm. Anal. Calcd. for $C_{35}H_{22}N_{61}$, 0.5 H_2O : C, 78.49 ; H, 4.33 ; N, 15.69. Found : C, 79.02 ; H, 4.21 ; N, 15.68.

Compound **8** : mp 350°C ; ^1H nmr (200 MHz, $CDCl_3$) δ (ppm) : 8.48 (2H, s) ; 8.10 (2H, d, J = 5.8 Hz) ; 7.82 (2H, d, J = 5.5 Hz) ; 7.66 (4H, m) ; 7.40 (4H, m) ; 5.17 (d, 1H, J = 10 Hz) ; 5.07 (d, 1H, J = 10 Hz) ; 4.57 (2H, s) ; ms (FAB+, NBA, NaCl) : 460 $(M+1+Cl)^+$; 425 $(M+1)^+$; UV (EtOH) λ_{max} (ε) : 358.4 (15200) ; 265.4 (72600) ; 247 (81700) ; Anal. Calcd. for $C_{29}H_{20}N_4$: C, 82.05 ; H, 4.75 ; N, 13.2. Found: C, 81.51 ; H, 4.75; N, 13.09.

8. The assignments of the *endo* and *exo* protons for compound **8** were carried out by irradiation experiments.The signal at higher field was attributed to the *exo* proton.
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10. After extraction and purification on silica gel column the yields in Tröger's bases drop to 60 %. The loss of products are mainly due to the low solubility of the Tröger's bases in organic solvents.

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