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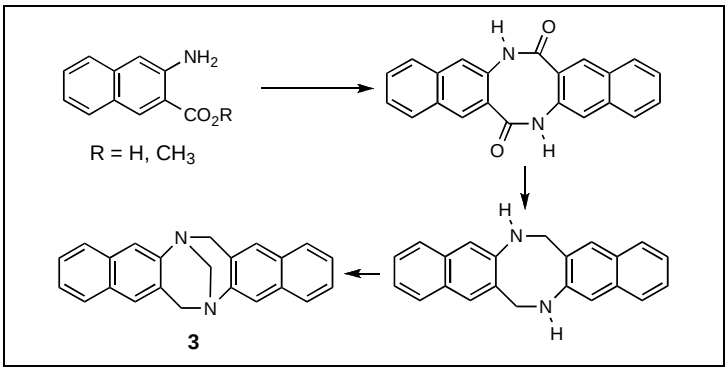
‡ **Dedicated to Prof. Charles W. Rees, in memoriam**



The title compound **3** was prepared in four steps from commercial 3-amino-2-naphthoic acid in an overall 75 % yield. Attempts to use the same approach in the case of 2-aminonicotinic acid methyl ester failed. All the compounds were characterized by NMR.

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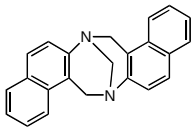
INTRODUCTION

In 1964, Farrar [1] described, for the first time, the reaction of β-naphthylamine and formaldehyde in the presence of hydrochloric acid. According to this author, the three possible regioisomers **1**-**3** of the corresponding Tröger's base were formed although they were not identified.

Later, Tálas *et al.* [2] repeated the reaction determining that "the three isolated regioisomers" are the same compound, the **bent** Tröger's base (TB) **1**. This is due to the lower reactivity of the β position in naphthalenes; besides, obtaining **bent** isomers instead of **linear** ones is the usual result found in benzazines [3] and acridines [4,5]. For the same reason TB **4** cannot be prepared from α-naphthylamine (present authors unreported experiments).



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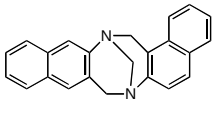

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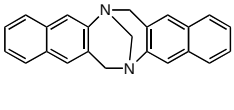

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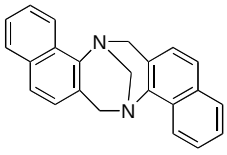

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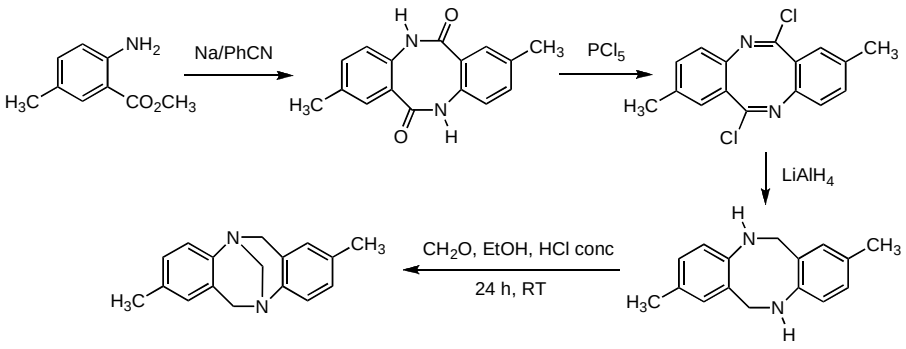
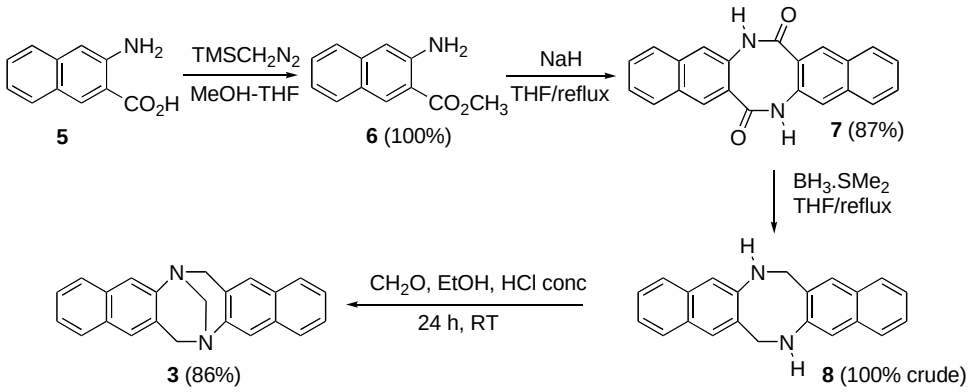
Scheme 1



Scheme II



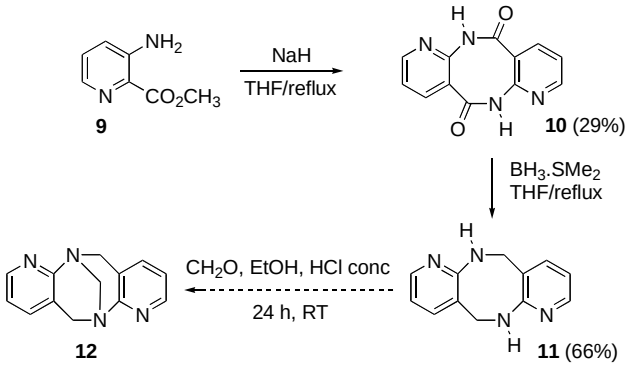
RESULTS AND DISCUSSION

We decided to attempt the synthesis of the **linear** TB **3** adapting the indirect method developed by Cooper and Partrige in 1955 for Tröger's Base (2,8-dimethyl-6*H*-12*H*-5,11-methano-dibenzo[*b*,*f*][1,5]diazocine) (Scheme I) [6].

We have adapted this process, avoiding the chlorinated intermediate, to prepare the unknown TB **3** in excellent yield (Scheme II).

The success obtained in the preparation of **3** prompted us to try the same synthetic procedure for preparing the still unknown TB **12** [3] derived from 2-aminonicotinic acid methyl ester (**9**) (Scheme III). However, the yield in diazocinedione **10** (several attempts) was much lower than that of **7** (Scheme II) and, moreover, all our different approaches to transform **11** into **12** failed: higher temperatures, longer reaction times, higher amounts of hydrochloric acid or heating **11** in anhydrous DMSO at 80 ºC bubbling HCl (g) during 24 hours [7].

Scheme III



NMR Results. All the compounds reported in Schemes II and III have been identified by NMR

In what concerns the ^{1}H-NMR spectrum of the bis-amide **7**, the more shielded singlet shows a NOE correlation with the NH and with another aromatic proton, allowing to assign the first one to H-5 and the second one to H-4. The remaining singlet and doublet are H-8(16) and H-1, respectively. Finally, a ^{1}H-^{1}H COSY correlation allows for the assignment of signals corresponding to protons H-2 and H-3 by correlation with H-1 and H-4, respectively.

In the case of the bis-amide **10** derived from the 2-aminonicotinic acid methyl ester, the assignment is immediate from the values of the coupling constants. Thus, the most shielded double doublet with couplings of 7.7 and 4.8 Hz corresponds to H-3, with $^3J_{3,4} > {}^3J_{2,3}$, as usual in pyridine derivatives [8]. These values of the coupling constants allow for the assignment of H-2 and H-4. The order of chemical shifts we have determined ($\delta 2 > \delta 4 > \delta 3$) is that found in most pyridines [8].

In the corresponding ^{13}C NMR spectra, the assignments are based on 2D ^{1}H-^{13}C experiments: HMQC for CH carbons with $^1J \approx 150$ Hz and HMBC for quaternary carbons with $^nJ \approx 8$ Hz.

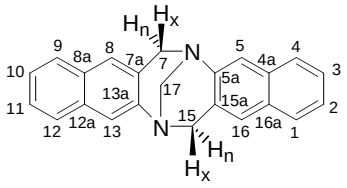
The ^{1}H NMR spectrum of bis-amine **8** in DMSO-d_6 shows some interesting features. The NH signal of amide **7** has disappeared and the characteristic triplet of an amino group coupled with the adjacent methylene is observed. However, the expected multiplet of the methylene is not found, probably being too broad. This is related to the conformational mobility of **8** as we have shown for similar systems [9]. In $CDCl_3$, the coupling with the NH disappears (fast exchange) and the AB system of the methylene is observed at 4.56 and 5.15 ppm, $^2J_{gem} = 17.3$ Hz. A similar behaviour is observed in bis-amine **11**.

Tröger's Bases, due to their C_2 axis of symmetry, show in their ^{1}H-NMR spectra only half of the signals. Besides the aromatic protons, the part corresponding to the aliphatic protons of the central diazocine ring is very characteristic, with a singlet for the methylene bridge protons (H-17) and AB system for the *endo* and *exo* protons of the methylene at position 7 (and 15). To assign these protons we have used the rule that *endo* protons are generally more shielded than the *exo* ones, due to the shielding cone of the aromatic rings [10]. Besides, there is an HMBC correlation between the most deshielded proton of the doublet and C-5a (13a) proving that this signal corresponds to H-7x(15x) [11].

The aromatic part of the spectrum has been assigned in the following way. Irradiation of the singlet at 7.48 ppm shows a NOE correlation with the *endo* and *exo* protons, thus it corresponds to the spatially close H-8(16). A correlation with the doublet at 7.66 ppm is also observed, thus it is H-1(9) and, consequently, the other doublet corresponds to H-4(12). Finally, the signals belonging to H-2(10) and H-3(11) have been assigned by a COSY experiment that relates H-1(9) and H-4(12) with H-2(10) and H-3(11), respectively.

The ^{13}C-NMR spectra have been assigned, as previously, by HMQC and HMBC 2D correlations. In the HMBC experiment, a two-bond correlation between the quaternary carbon C-7a(15a) and the methylene protons H-7x(15x) and H7n(15n) appears. Another correlation is observed between C-17 and the H-7n(15n) situated in a zig-zag disposition [11].

The NMR parameters of TB **3** are reported in Tables 1 (^{1}H) and 2 (^{13}C and the observed ^{1}H-^{13}C correlations).



3

Table 1

^{1}H-NMR of TB **3** (δ in ppm and J in Hz) in DMSO-d_6

δ(H-1)	7.66	$J_{1,2}$	7.9
δ(H-2)	7.28	$J_{2,3}$	6.3
δ(H-3)	7.35	$J_{3,4}$	8.2
δ(H-4)	7.76	$J_{7n,7x}$	16.7
δ(H-5)	7.67		
δ(H–7n)	4.52		
δ(H–7x)	4.97		
δ(H–8)	7.48		
δ(H–17)	4.46		

Table 2

^{13}C chemical shifts (δ en ppm) of TB **3** and ^{1}H-^{13}C heteronuclear correlations

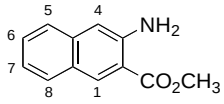
		heteronuclear correlations		
carbon	δ	^1J	^3J	^2J
1	126.93	H-1	H-3, H-16	
2	124.49	H-2	H-4	
3	125.38	H-3	H-1	
4	126.70	H-4	H-2, H-5	
4a	132.53	-	H-1, H-3, H-16	
5	121.39	H-5	H-4	
5a	146.96	-	, H-16, H-7x, H-17	
7	60.25	H-7n, H-7x	H-8, H-17	
7a	128.22	-	H-13	H-7n, H-7x
8	125.20	H-8	H-9	
8a	129.94	-	H-10, H-12, H-13	
17	66.46	H-17	H-7n	

EXPERIMENTAL

Purification and separation of the reaction products were carried out by flash chromatography over silica gel (Merck 230-400 mesh) while TLC (silica gel 60 F_{254}/aluminium sheets) was used to monitor the reactions. Melting points were determined in capillary tubes using a Gallenkamp apparatus. IR spectra were registered on a Perkin-Elmer 781 spectrometer.

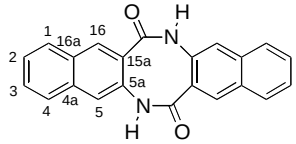
^{1}H and ^{13}C NMR spectra were recorded on Varian XL-300 S (^{1}H 300 MHz), Bruker 250-AM (^{1}H 250 MHz), Bruker AM-300 (^{1}H 300 MHz) and Bruker AV-500 (^{1}H 500 MHz) using TMS as internal reference. Different 2D techniques were used when necessary (COSY, HMBC, HMQC) as well as NOE experiments.

3-Amino-2-naphthalenecarboxylic acid methyl ester (**6**).



Under Ar atmosphere, 2.67 mmol (500 mg) of acid **5** were dissolved in 2.66 mL of anhydrous THF and 1.77 mL of anhydrous MeOH. Then 2.37 mL of 2 *M* trimethylsilyl-diazomethane in diethyl ether were slowly added with a small increase of the solution temperature. The brown solution was kept under agitation for 24 h at RT. The solution was evaporated under reduced pressure obtaining 546 mg of a yellow solid which is pure according to NMR. Yield 100%. Mp. 88-90 ºC. Lit. mp 102 (hexane) [12]. IR (KBr) ν (cm^{-1}): 3497, 3389, 1695, 1630, 1590, 1570, 1533, 1506, 1464, 1437, 1350, 1286, 1211, 1196, 1146, 1132, 841, 791, 748. ^{1}H RMN (DMSO-d_6) δ (ppm): 3.87 (s, 3H, OCH_3), 6.42 (s, 2H, NH_2), 7.03 (s, 1H, H-4), 7.14 (ddd, 1H, $^3J_{7,8}$ = 8.0 Hz, $^3J_{6,7}$ = 7.0 Hz, $^4J_{5,7}$ = 1.0, H-7), 7.38 (ddd, 1H, $^3J_{5,6}$= 8.4, $^3J_{6,7}$ = 6.7, Hz, $^4J_{6,8}$ = 1.0, H-6), 7.52 (d, 1H, $^3J_{5,6}$ = 8.5 Hz, H-5), 7.77 (d, 1H, $^3J_{7,8}$ = 7.8, H-8), 8.43 (s, 1H, H-1) ^{13}C RMN (DMSO-d_6) δ (ppm): 52.08 (CH_3), 108.98 (C-4), 113.85 (C-2), 122.00 (C-7), 124.88 (C-5), 124.93 (C-9), 128.93 (C-6), 129.32 (C-8), 132.85 (C-1), 137.18 (C-10), 146.92 (C-3), 167.76 (CO).

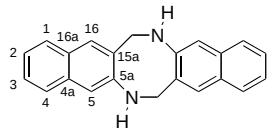
6*H*-14*H*-Dinaphtho[2,3-*b*:2',3'-*f*][1,5]diazocine-7,15-dione (**7**).



Ester **6** (1.085 mmol, 218 mg) was added to 2.86 mmol (114 mg) of 60% sodium hydride in suspension in oil covered by anhydrous THF. The mixture was refluxed for 24 h becoming dark brown. Then, 5% hydrochloric acid was added until acid pH, finally water was added and a brown solid precipitates and was collected by filtration, obtaining 194 mg of the crude bis-

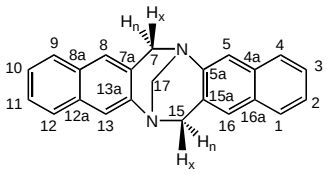
amide **7**. The crude was chromatographed using as eluent ethyl acetate/hexane 9:1. Pale brown pure amide was obtained (98 mg, yield 53%). The reaction was repeated starting from 2.72 mmol (546 mg) of ester **6** and 492 mg of amide pure enough to continue the synthesis was obtained (yield 100%). Mp: > 300 ºC (dec.). IR (KBr) ν (cm^{-1}): 3167, 3053, 2922, 1655, 1387, 1308, 1267, 1236, 752. ^{1}H RMN (DMSO-d_6) δ (ppm): 7.46 (td, 1H, $^3J_{app}$ = 6.7 Hz, $^4J_{2,4}$ = 1.3 Hz, H-2), 7.50 (td, 1H, $^3J_{app}$ = 6.5 Hz, $^4J_{1,3}$ = 1.3 Hz, H-3), 7.65 (s, 1H, H-5), 7.85 (d, 1H, $^3J_{3,4}$ = 7.4 Hz, H-4), 7.90 (d, 1H, $^3J_{1,2}$ = 7.3 Hz, H-1), 7.95 (s, 1H, H-8(16)), 10.50 (s, 1H, NH). ^{13}C RMN (DMSO-d_6) δ (ppm): 124.02 (C-5), 126.77 (C-2), 127.37 (C-4), 127.69 (C-3), 127.86 (C-8(16)), 127.93 (C-1), 131.17 (C-16a), 131.73 (C-4a), 133.12 (C-5a), 133.36 (C-15a), 169.56 (CO). *Anal.* Calcd. for $C_{22}H_{14}N_2O_2$: C, 78.09; H, 4.17; N, 8.28.Found: C, 77.88; H, 4.33; N, 8.30.

6*H*-7*H*-14*H*-15*H*-Dinaphtho[2,3-*b*:2',3'-f][1,5]diazocine (**8**).



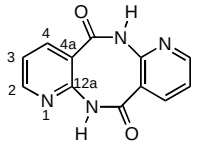
To 0.176 mmol (60 mg) of bis-amide **7** was added first 1.47 mL of anhydrous THF and then slowly and at 0 ºC, 1.179 mmol (118 µL) of 10 *M* BH_3SMe_2. The mixture is refluxed for 17 h resulting in a transparent solution. 6 *M* hydrochloric acid at 0 ºC was added to destroy the borane, the solution was stirred 3 h and 15 *M* ammonium hydroxide was added at 0 ºC until the solution becomes basic. Then, it was extracted by dichloromethane (3 times 10 mL), the organic layer is washed with water and dried over anhydrous $MgSO_4$. After the solvent was evaporated, 58 mg of bis-amine **8** almost pure was obtained and used as such in the following reaction (attempts to purify the compound by column chromatography result in partial decomposition). Yield 100%. Mp 275-277 ºC. ^{1}H RMN (DMSO-d_6) δ (ppm): 6.31 (bt, 1H, ^3J = 6.9 Hz, NH), 6.91 (s, 1H, H-5), 7.08 (td, 1H, ^3J = 7.4 Hz, $^4J_{2,4}$ = 1.5 Hz, H-2), 7.23 (td, 1H, ^3J = 7.4 Hz, $^4J_{1,3}$ = 1.5 Hz, H-3), 7.44 (bd, 1H, $^3J_{3,4}$ = 8.6 Hz, H-4), 7.54 (bs, 1H, H-8(16)), 7.62 (bd, 1H, $^3J_{1,2}$ = 8.6 Hz, H-1). *HRMS(EI)* Calcd. for $C_{22}H_{18}N_2$: 310.14700. Found: 310.14721.

7*H*-15*H*-6,14-Methanodinaphtho[2,3-*b*:2',3'-*f*][1,5]diazocine (**3**).



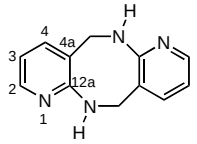
To 0.187 mmol (58 mg) of bis-amine **8** were added, under Ar atmosphere, 2.3 mmol (157 µl) of 35-40% formaldehyde, 1.5 mL of anhydrous ethanol and finally, with care, 393 µL of 6 *M* hydrochloric acid. The suspension becomes pale brown with an increase of the temperature. It was stirred for 64 h at RT. Then the solution is made basic with 25% ammonium hydroxide. Water was added and the aqueous solution extracted with dichloromethane (3 times 10 mL), the organic layer dried over anhydrous $MgSO_4$ and the solvent evaporated under reduced pressure. The resulting TB **3** was obtained as a brown solid, yield 52 mg, 86%. Mp 213-215 ºC. IR (KBr) ν (cm^{-1}): 3422, 2924, 2852, 2345, 1499, 1458, 748. *Anal.* Calcd. for $C_{23}H_{18}N_2$: C, 85.68; H, 5.63; N, 8.69. Found: C, 85.86; H, 5.43; N, 8.77. *HRMS(EI)* Calcd. for $C_{23}H_{18}N_2$: 322.14699. Found: 322.14653.

6*H*-12*H*-Dipyrido[2,3-*b*:2',3'-*f*][1,5]diazocine-5,11-dione (**10**).



Ester **9** (0.921 mmol, 140 mg) was added to 2.43 mmol (97 mg) of 60% sodium hydride in suspension in oil covered by anhydrous THF. The resulting suspension was refluxed 24 h and then acidified with 5% hydrochloric acid. By adding water, bis-amide **10** precipitates: 25 mg, 25% yield. A second reaction starting from 3.72 mmol (566 mg) of **9** affords 128 mg of pure **10**, yield 29%. Mp: > 300 ºC (dec.). IR (KBr) ν (cm^{-1}): 3238, 3177, 3057, 2922, 1655, 1589, 1576, 1481, 1429, 1385. ^{1}H RMN (DMSO-d_6) δ (ppm): 7.34 (dd, 1H, $^3J_{3,4}$ =7.7 Hz, $^3J_{2,3}$ = 4.8 Hz, H-3), 7.86 (dd, 1H, $^3J_{3,4}$= 7.7 Hz, $^4J_{2,4}$ = 1.8 Hz, H-4), 8.47 (dd, 1H, $^3J_{2,3}$= 4.8 Hz, $^4J_{2,4}$ = 1.8 Hz, H-2), 10.94 (bs, 1H, NH). ^{13}C RMN (DMSO-d_6) δ (ppm): 123.05 (C-3), 127.64 (C-4a), 138.35 (C-4), 147.11 (C-12a), 150.74 (C-2), 167.50 (CO). *Anal.* Calcd. for $C_{12}H_8N_4O_2$: C, 60.00; H, 3.36; N, 23.32. Found: C, 59.87; H, 3.21; N, 23.57.

5*H*-6*H*-11*H*-12*H*-Dipyrido[2,3-*b*:2',3'-*f*][1,5]diazocine (**11**).



Careful addition of 0.556 mmol (55.6 µL) of 10 *M* BH_3SMe_2 to a solution of 0.083 mmol (20 mg) of bis-amide **10** in 1 mL of anhydrous THF and then 17 h reflux of the resulting solution results in a transparent solution. The borane in excess is destroyed by treating the solution with 6 *M* hydrochloric acid. Then the stirring is maintained for 3 h, 15 M ammonium hydroxide is added at 0 ºC till basic pH. The solution is extracted with dichloromethane (3 times 10 mL), the organic layer is washed with water and dried over anhydrous $MgSO_4$. By evaporation of the solvent, 11 mg of the bis-amine **11** is obtained that is pure enough to be used without further purification. ^{1}H RMN (DMSO-d_6) δ (ppm): 6.52 (dd., 1H, $^3J_{3,4}$ = 7.1 Hz, $^3J_{2,3}$ = 4.9, H-3), 6.58 (bt, ^3J = 8.5 Hz,1H, NH), 7.27 (dd, 1H, $^3J_{3,4}$ = 7.1 Hz, $^4J_{2,4}$ =1.7 Hz, H-4), 7.84 (dd, 1H, $^3J_{2,3}$ = 4.9 Hz, $^4J_{2,4}$ = 1.7 Hz, H-2). *HRMS(EI)* Calcd. for $C_{12}H_{12}N_4$: 212.10620. Found: 212.10833.

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