Synthesis and spectroscopy of the Tröger's base derived from 2-aminoacridine

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Dedicated to Professor Miha Tisler on his 75th anniversary
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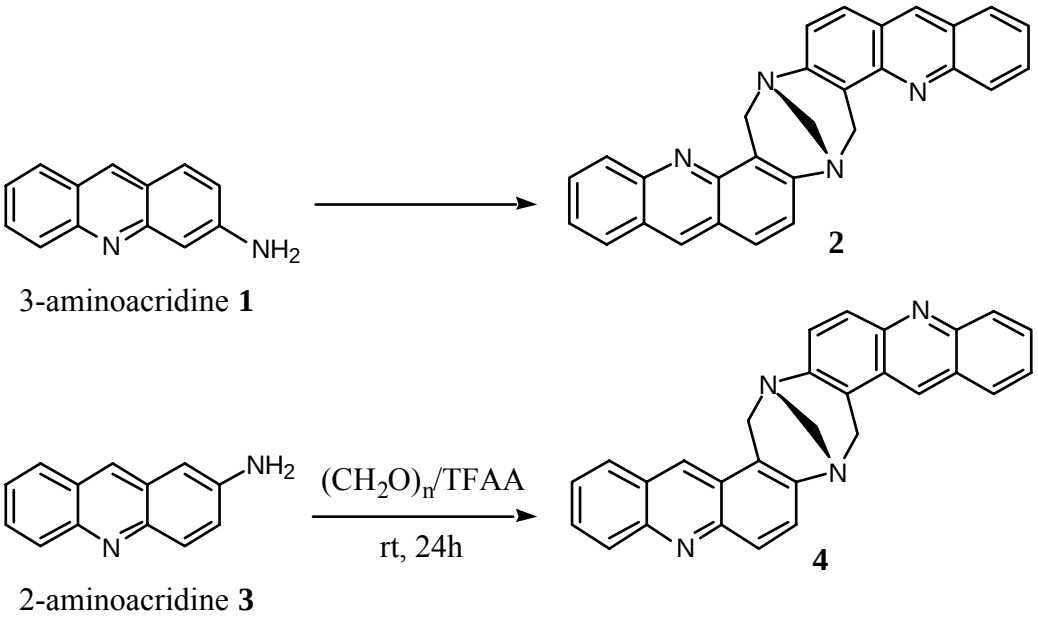
Abstract
The analogs of the Tröger's base, 7,17-methano-6,7,16,17-tetrahydrodiacridino-[3,4-*b*:3',4'-*f*]-[1,5]-diazocine was prepared starting from 2-aminoacridine instead of 3-aminoacridine. The new compound, 7,17-methano-6,7,16,17-tetrahydro-diacridino-[2,1-*b*:2',1'-*f*]-[1,5]-diazocine, has been fully characterized by ^{1}H- and ^{13}C- NMR spectroscopies using mono- and bi-dimensional techniques. Other aminoacridine derivatives failed to afford Tröger's bases.

Keywords: Tröger's bases, 2-aminoacridine, NMR, ^{1}H NMR, ^{13}C NMR

Introduction

Some years ago, Lhomme and his coworkers described the synthesis of the Tröger's base analog, 7,17-methano-6,7,16,17-tetrahydrodiacridino-[3,4-*b*:3',4'-*f*]-[1,5]-diazocine, **2,** from 3-amino-acridine **1**[1,2] and reported its NMR properties[3] and X-ray structure (see Scheme 1).[4] Most important is the fact that this compound interacts differently with DNA than do other intercalants.[5] Then, some of the same workers extended the synthesis and biological studies to other, but always 3-amino- substituted, acridines.[6,7]

Owing to our interest in Tröger's bases[8–11] and in aminoacridines,[12–14] we decided to study the reactivity of these last compounds towards formaldehyde in acid media. Only with 2-aminoacridine, **3**, were we successful in obtaining the Tröger's base, **4**.



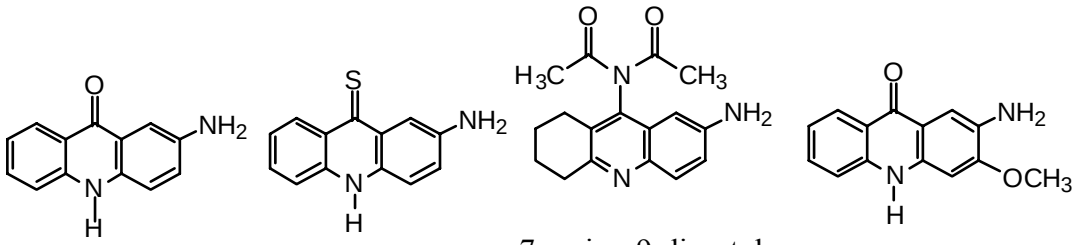
Scheme 1

Results and Discussion

Chemistry

Compound **4** was prepared according to the method of Tatibouët, Demeunynck and Lhomme[15] from 2-aminoacridine, trifluoroacetic acid, and paraformaldehyde under argon for 24 h at room temperature. The compound was obtained only in 45% yield (isomer **2** was obtained in 90 % yield).[1,2]

We carried out similar reactions with the compounds of Scheme 2.



2-aminoacridin-9-one **5**

2-aminothioacridin-9-one **6**

7-amino-9-diacetyl-amino-1,2,3,4-tetra-hydroacridine **7**

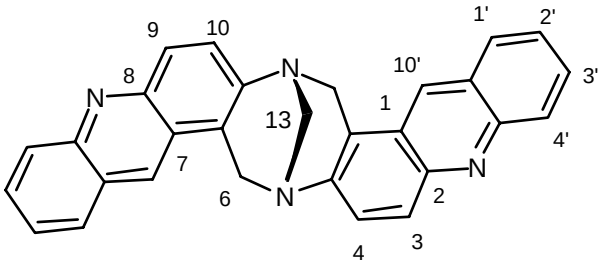
2-amino-3-methoxy-acridin-9-one **8**

Scheme 2

In no case were Tröger's bases identified; only intermediate compounds were isolated, in very low yields.

NMR spectroscopy

We have gathered in Tables 1 and 2 all the information available on compound **4**. The protons of the methylene group at position 6 are named 6n (*endo*) and 6x (*exo*). We are using the numbering of Tröger's base:



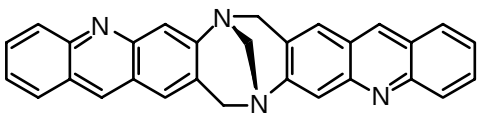
4

The aromatic protons were assigned using double resonance and NOEDIF experiments. The ^{13}C NMR spectrum was assigned using first a DEPT experiment to identify the quaternary carbon atoms and then 2-dimensional ^{13}C–^{1}H HMQC (one bond)- and HMBC (long distance) correlations.

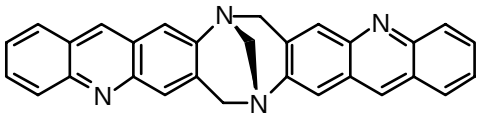
The assignments in Table 2 are consistent both with other publications dealing with Tröger's bases, [8,10] or with acridines.[12–14]

Conclusions

The formation of Tröger's bases from aminoacridines and their derivatives (acridin-9-ones, acridin-9-thiones) is a reaction of limited scope. Both **2** and **4** are "bent" isomers, which is the normal result in acridines:[16–20] they cyclize towards the *peri*- position. For the moment, there is no hope of obtaining "linear" compounds such as **2b** and **4b**, that would be very interesting scaffold structures.



2b



4b

Table 1. ^{1}H NMR data (δ ppm, J Hz) of compound **3** in $CDCl_3$

Proton	δ	Multiplicity	J

H-6n	4.90	d	$^{2}J_{6n,6x} = 16.8$
H-6x	5.15	d	
H-13	4.61	s	
H-3	8.06	d	$^{3}J_{3,4} = 9.3$
H-4	7.68	d	
H-1’	7.97	d	$^{3}J_{1',2'} = 8.4$
H-2’	7.53	m	$^{3}J_{2',3'} = 7.0$; $^{4}J_{2',4'} = 1.2$
H-3’	7.75	m	$^{4}J_{1',3'} = 1.5$
H-4’	8.16	d	$^{3}J_{3',4'} = 8.5$
H-10’	8.58	s	

Table 2. ^{13}C NMR data (δ ppm) and ^{13}C–^{1}H correlations of compound **3** in $CDCl_3$

Carbon	DEPT	HMQC	HMBC	δ
C-1	---	---	8.06	124.9
C-2	---	---	8.58, 7.68	147.4
C-3	CH	8.06	---	129.5
C-4	CH	7.68	---	129.8
C-4a	---		5.15, 4.90, 4.61, 8.06	144.4
C-6	CH_2	5.15, 4.90	4.61	54.5
C-13	CH_2	4.61	4.90	67.0
C-6a	---	---	5.15, 4.90, 7.68, 8.58	120.4
C-1’	CH	7.97	8.58	128.0
C-2’	CH	7.53	7.68	126.1
C-3’	CH	7.75	7.97	129.8
C-4’	CH	8.16	7.53	129.1
C-4a’	---	---	8.58, 7.97	147.8
C-10’	CH	8.58	7.97	128.9
C-10a’	---	---	7,53, 8.16	126.3

Experimental Section

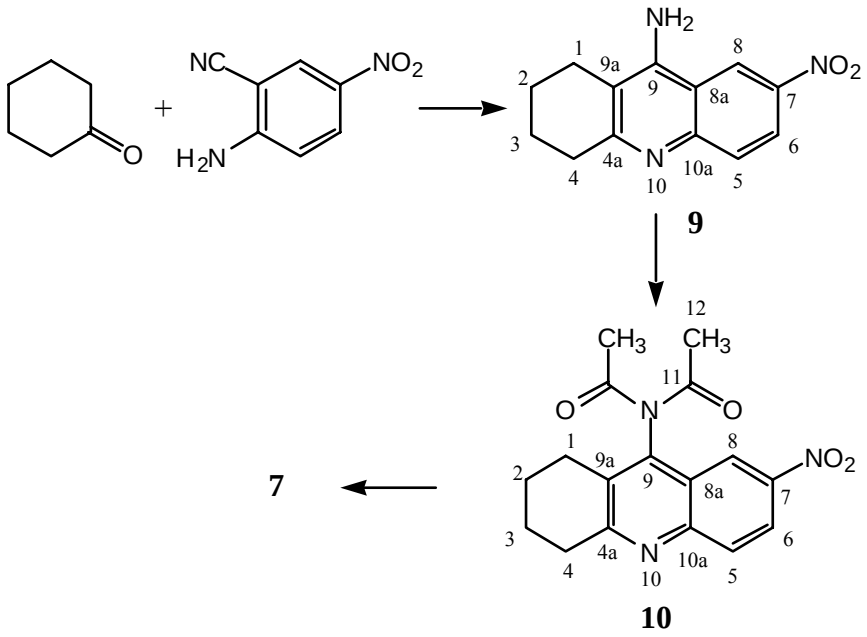
General Procedures. Melting points were determined with a hot-stage microscope and are uncorrected. Column chromatography was performed on silica gel (Merck 60, 70–230 mesh). NMR spectra were recorded on a Bruker AC 200 (200.13 MHz for ^{1}H, and 50.32 MHz for ^{13}C) and Bruker Avance-300 (300.13 MHz for ^{1}H and 75.48 MHz for ^{13}C) spectrometers using standard conditions. Chemical shifts (δ, in ppm) are referred to internal Me_4Si. Mass spectra (HRMS) at 70 eV, using the electron-impact mode, were obtained on a VG Autospec spectrometer by “Laboratorio de Espectrometría de Masas-UAM, Madrid”.

Syntheses

The following compounds have been described by some of us in previous publications: 2-aminoacridine **(3),**[21] 2-aminoacridin-9-one (**5**),[21] and 2-aminoacridin-9-thione (6).[22]

Synthesis of compound 7

7-Nitro-1,2,3,4-tetrahydro-9-acridinylamine (9). 5-Nitroanthranilonitrile (1.63 g, 10 mmol), cyclohexanone (1.1 g, 11 mmol), and sodium-dried toluene (50 mL) were placed in a two-necked round- bottomed flask. Boron trifluoride diethyl etherate (1.56 g, 11 mmol) was added slowly via syringe, and the mixture heated under reflux for 24 h. On cooling, a yellow precipitate appeared, which was filtered and washed with water. The product was crystallized from NaOH 1*M* (100mL). After filtration the product **11** was recovered pure (2.3 g, yield 94%, m.p. 261 °C. Lit. 264–266 °C).[23] ^{1}H- NMR (DMSO-d_6, δ): 1.76 [bs, 4H, (2-CH_2)-2,3], 2.49 [bs, 2H, (CH_2)-1], 2.79 [bs, 2H, (CH_2)-4], 6.95 (s, 2H, NH_2), 7.65 (d, 1H, J = 8.8 Hz, CH-5), 8.10 (d, 1H, J = 8.8 Hz, CH-6), 9.23 (d, 1H, J = 2.2 Hz, CH-8). ^{13}C NMR (DMSO-d_6, δ): 22.36 and 22.48 (C-2 and C-3), 23.78 (C-1), 33.96 (C-4), 110.73 (C-8a), 115.56 (C-9a), 120.65 (C-8), 121.42 (C-6), 129.52 (C-5), 142.07 (C-7), 149.28 (C-5a), 150.68 (C-9), 161.56 (C-4a). Anal. Calcd. for $C_{13}H_{13}N_3O_2$: C, 64.19; H, 5.39; N, 17.27. Found: C, 64.01; H, 5.43; N, 17.22%.

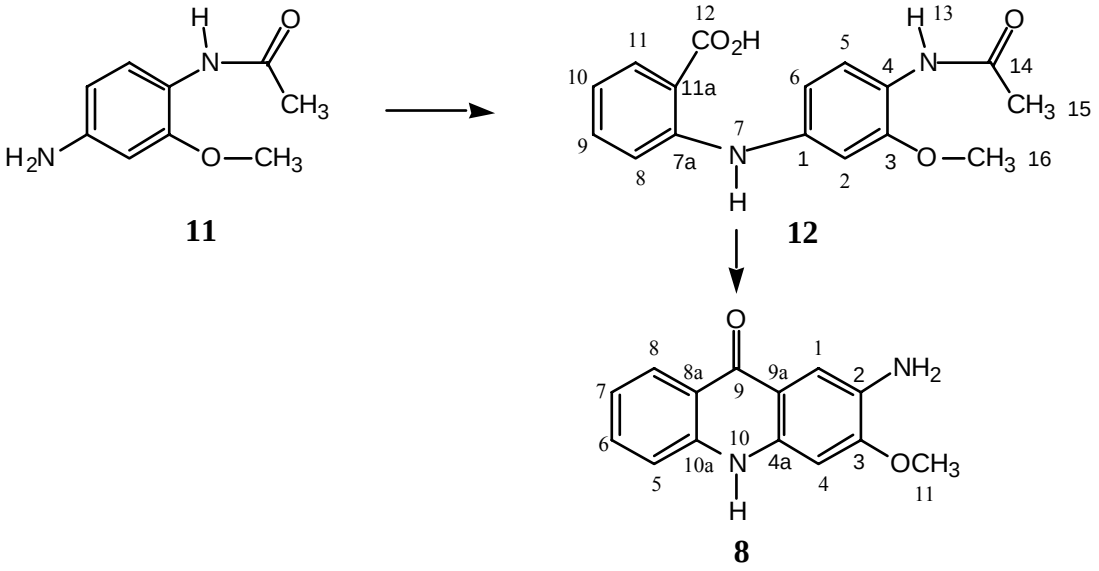


***N*-Acetyl-*N*-(7-nitro-1,2,3,4-tetrahydro-9-acridinyl)acetamide (10).** Compound **9** (1 g, 4.11 mmol) and sodium acetate (0.67 g, 8.22 mmol) were dissolved in acetic anhydride (40 mL), and stirred under reflux for 3 h. The reaction was monitored by TLC (dichloromethane:methanol, 9:1). The mixture was filtered and the filtrate poured onto crushed ice and neutralized with 3*M* NaOH. The yellow needles of **10** were recovered by filtration (1.1 g, yield 79%, m.p. 166 °C). ^{1}H NMR (DMSO-d_6, δ): 1.85 [m, 4H, (2-CH_2)-2 and 3], 2.25 [s, 6H, (2 CH_3)-12], 2.68 [t, 2H, J = 6.3 Hz, (CH_2)-1], 3.12 [t, 2H, J = 6.3 Hz, (CH_2)-4], 8.16 [d, 1H, J = 9.3 Hz, CH-5], 8.39 (dd, 1H, J = 1.6,

8.8 Hz, CH-6], 8.63 (d, 1H, J = 1.6 Hz, CH-8]. ^{13}C NMR (DMSO-d_6, δ): 21.54 and 21.92 (C-2 and C-3), 24.67 (C-1), 26.15 (C-12), 33.93 (C-4), 119.16 (C-8), 122.94 (C-6), 123.74 (C-8a), 130.87 (C-5), 131.70 (C-9a), 143.38 (C-9), 145.96 (C-7), 148.77 (C-5a), 165.21 (C-10a), 171.90 (C-11). Anal. Calcd. for $C_{17}H_{17}N_3O_4$: C, 62.38; H, 5.23; N, 12.84. Found: C, 62.31; H, 5.23; N, 12.78%.

***N*-Acetyl-*N*-(7-amino-1,2,3,4-tetrahydro-9-acridinyl)acetamide (7).** Compound **10** (1.4 g, 4.7 mmol) and Pd/C catalyst in ethanol (100 mL) were stirred vigorously under an H_2 atmosphere for 2 h. After filtration, the solvent was removed under vacuum to give **7** as an orange powder (0.72 g, yield 84%, m.p. 173 °C). ^{1}H NMR (DMSO-d_6, δ): 1.77 [m, 2H, (CH_2)-3], 1.84 [m, 2H, (CH_2)-2], 2.03 [s, 6H, (2-CH_3)-12], 2.56 [t, 2H, J = 6.4 Hz, (CH_2)-1], 2.96 [t, 2H, J = 6.4 Hz, (CH_2)-4], 5.66 [s, 2H, (NH_2)-7], 6.52 (d, 1H, J = 2.3 Hz, CH-8), 7.12 (dd, 1H, J = 8.9, 2.3 Hz, CH-6), 7.66 (d, 2H, J = 8.9 Hz, CH-5). ^{13}C NMR (DMSO-d_6, δ): 21.98 (C-3), 22.56 (C-2), 24.42 (C-1), 25.82 (C-12), 32.86 (C-4), 98.09 (C-8), 121.55 (C-6), 125.98 (C-8a), 128.22 (C-9a), 129.61 (C-5), 138.71 (C-9), 141.43 (C-10a), 147.87 (C-7), 153.50 (C-4a), 171.83 (C-11). Anal. Calcd. for $C_{17}H_{19}N_3O_2$: C, 68.67; H, 6.44; N, 14.13. Found: C, 68.59; H, 6.39; N, 14.25%.

Synthesis of compound 8



2-[4-(Acetylamino)-3-methoxyanilino]benzoic acid (12). 3-Methoxy-4-acetamidoaniline (**11**, 1.8 g, 10 mmol), 2.21 g of *o*-bromobenzoic acid (11 mmol), 1.65 g of anhydrous potassium carbonate (12 mmol), 0.05 g of powdered copper[24] and 15 mL of ethyl methyl ketone were placed in a 250 mL round- bottomed flask, and sonicated in a bath at 80 °C for 3 h. After removal of the solvent under vacuum, the brown residue was stirred in 80 mL of hot water, filtered and acidified to pH 5 with 2 *M* aqueous hydrochloric acid. The green precipitate of **15** was filtered off, washed with water, and dried (1.9 g, m.p. 234 °C, yield 63%). ^{1}H NMR (DMSO-d_6, δ): 2.06 [s, 3H, (CH_3)-15], 3.81 [s, 3H, (CH_3)-16], 6.77 (m, 2H, CH-5,10), 6.90 (brs, 1H, CH-2), 7.33 (brs, 1H, CH-9), 7.36 (brd, 1H, J = 8.2 Hz, CH-8), 7.84 (m, 2H, CH-6,11), 9.11 (s, 1H, NH-13). ^{13}C NMR (DMSO-d_6, δ): 23.90 (C-15),

55.86 (C-16), 105.98 (C-2), 1113.55 (C-8), 114.15 (C-6), 117.46 (C-4), 123.32 (C-5 and C-11), 131.87 (C-10), 134.44 (C-9), 137.05 (C-1 and C-7a), 150.90 (C-3), 168.47 (C-12 and C-14). Anal. Calcd. for $C_{16}H_{16}N_2O_4$: C, 63.99; H, 5.37; N, 9.33. Found: C, 64.02; H, 5.39; N, 9.54%.

2-Amino-3-methoxy-9(10*H*)-acridinone (8). Cyclization of **12** with H_2SO_4 gave only the 2-amino-3-methoxyacridine-9(10*H*)-one **8**, the acetyl group being lost during the acidic treatment. 2-[4-Acetylamino-3-methoxyanilino]benzoic acid **12** (1 g, 3.3 mmol) and sulfuric acid (96%) (10 ml) were stirred for 3 h at 100°C, then poured onto ice (100 g) and neutralized with diluted ammonia (10%). The green precipitate was washed with water and dried, then the green powder **8** was crystallized from hot ethanol (95%) (0.7 g, m.p. > 300 °C. Yield 87 %). ^{1}H NMR (DMSO-d_6, δ): 3.92 [s, 3H, (CH_3)-11], 4.92 (s, 2H, NH_2), 6.85 (s, 1H, CH-4), 7.13 (td, 1H, J = 1.1, 7.7 Hz, CH-7), 7.39 (s, 1H, CH-1), 7.42 (dd, 1H, J = 1.1, 7.15 Hz, CH-5), 7.58 (td, 1H, J = 1.1, 8.2 Hz, CH-6), 8.15 (dd, 1H, J = 1.1, 7.7 Hz, CH-8), 11.41 (s, 1H, NH-10). ^{13}C NMR (DMSO-d_6, δ): 56.08 (C-11), 97.14 (C-4), 106.65 (C-1), 115.76 (C-9a), 117.29 (C-5), 119.85 (C-8a), 120.51 (C-7), 126.09 (C-8), 132.37 (C-6), 134.37 (C-4a), 135.33 (C-10a), 140.39 (C-2), 153.71 (C-3), 175.53 (C-9). Anal. Calcd. For $C_{14}H_{12}N_2O_2$: C, 69.99; H, 5.03; N, 11.66. Found: C, 70.10; H, 5.08; N, 11.74%.

7,17-Methano-6,7,16,17-tetrahydrodiacridino-[2,1-b:2',1'-f]-[1,5]-diazocine (4). To a solution of 2-aminoacridine (**3**, 200 mg, 1.03 mmol) in trifluoroacetic acid (5 mL) under Ar atmosphere was added 50 mg (1.65 mmol) of paraformaldehyde, with magnetic stirring. After 24 h stirring at r.t. the mixture was basified with 100 mL of 1*M* aq. sodium hydroxide. The aqueous layer was extracted with 3x50 mL of CH_2Cl_2 and the green-brown organic solution dried over Na_2SO_4, filtered, and evaporated at reduced pressure, affording 190 mg of a product that was purified by flash chromatography (eluent, ethyl acetate:hexane, 1:1): 95 mg of pure **4** was obtained (yield 45%), m.p. 270 °C (dec.), IR (KBr) ν 2924, 1624, 1526, 1466, 1427, 1205, 831 and 746 cm^{-1}. Exact mass: calc. 424.16878, found 424.16800.

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