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 1H- and 13C- NMR spectroscopies using mono- and bi-dimensional techniques. Other aminoacridine derivatives failed to afford Tröger’s bases.

Keywords: Tröger’s bases, 2-aminoacridine, NMR, 1H NMR, 13C 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-aminoacridine 1 and reported its NMR properties and X-ray structure (see Scheme 1). Most important is the fact that this compound interacts differently with DNA than do other intercalants. Then, some of the same workers extended the synthesis and biological studies to other, but always 3-amino-substituted, acridines.

Owing to our interest in Tröger’s bases and in aminoacridines, 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.
Results and Discussion

Chemistry

Compound 4 was prepared according to the method of Tatibouët, Demeunynck and Lhomme 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.
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:

![Diagram of compound 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.

![Diagram of compounds 2b and 4b]

Table 1.$^1$H NMR data ($\delta$ ppm, $J$ Hz) of compound 3 in CDCl$_3$

<table>
<thead>
<tr>
<th>Proton</th>
<th>$\delta$</th>
<th>Multiplicity</th>
<th>$J$</th>
</tr>
</thead>
</table>

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Table 2. $^{13}$C NMR data (δ ppm) and $^{13}$C–$^1$H correlations of compound 3 in CDCl$_3$

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<th>HMBC</th>
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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$_4$Si. 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), 2-aminoacridin-9-one (5), and 2-aminoacridin-9-thione (6).

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 (100 mL). After filtration the product 11 was recovered pure (2.3 g, yield 94%, m.p. 261 °C. Lit. 264–266 °C).

1H NMR (DMSO-d6, δ): 1.76 [bs, 4H, (2-CH2)-2,3], 2.49 [bs, 2H, (CH2)-1], 2.79 [bs, 2H, (CH2)-4], 6.95 (s, 2H, NH2), 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). 13C NMR (DMSO-d6, 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 C13H13N3O2: 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 3M NaOH. The yellow needles of 10 were recovered by filtration (1.1 g, yield 79%, m.p. 166 °C).

1H NMR (DMSO-d6, δ): 1.85 [m, 4H, (2-CH2)-2 and 3], 2.25 [s, 6H, (2 CH3)-12], 2.68 [t, 2H, J = 6.3 Hz, (CH2)-1], 3.12 [t, 2H, J = 6.3 Hz, (CH2)-4], 8.16 [d, 1H, J = 9.3 Hz, CH-5], 8.39 (dd, 1H, J = 1.6, J = 2.2 Hz, CH-11).
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8.8 Hz, CH-6], 8.63 (d, 1H, J = 1.6 Hz, CH-8). $^{13}$C NMR (DMSO-d$_6$, $\delta$): 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), 134.38 (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$_3$O$_4$: 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$_6$, $\delta$): 1.77 [m, 2H, (CH$_2$)$_3$-3], 1.84 [m, 2H, (CH$_2$)$_2$-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], 7.12 (dd, 1H, J = 2.3 Hz, CH-8), 7.12 (dd, 1H, J = 8.9 Hz, CH-6), 8.23 (d, 2H, J = 8.9 Hz, CH-5). $^{13}$C NMR (DMSO-d$_6$, $\delta$): 21.98 (C-3), 2 2.56 (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-8 a), 129.22 (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$_3$O$_2$: C, 68.67; H, 6.44; N, 14.13. Found: C, 68.59; H, 6.39; N, 14.25%.

Synthesis of compound 8

![Synthesis of compound 8](image)

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$_6$, $\delta$): 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$_6$, $\delta$): 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$_2$O$_4$: C, 63.99; H, 5.37; N, 9.33. Found: C, 64.02; H, 5.39; N, 9.54%.

2-Amino-3-methoxy-9(10H)-acridinone (8). Cyclization of 12 with H$_2$SO$_4$ gave only the 2-amino-3-methoxyacridine-9(10H)-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$_6$, $\delta$): 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$_6$, $\delta$): 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$_2$O$_2$: 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 1M aq. sodium hydroxide. The aqueous layer was extracted with 3x50 mL of CH$_2$Cl$_2$ and the green-brown organic solution dried over Na$_2$SO$_4$, 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.

References