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Spiro Tröger's Base Derivatives: Another Structural Phoenix?

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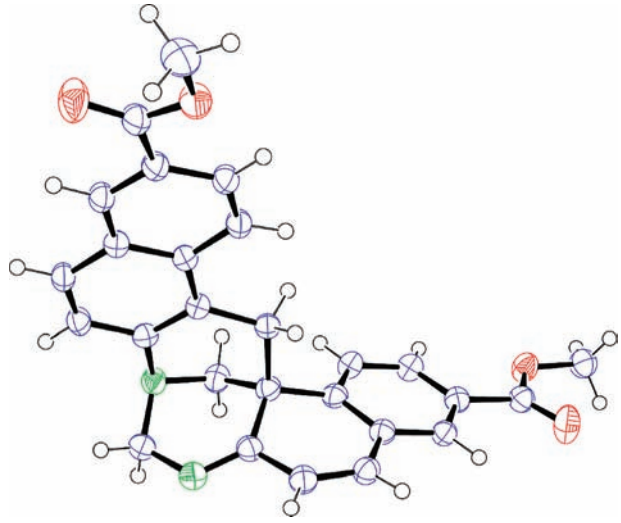
ABSTRACT



Recently, naphthalenoide derivatives of Tröger's base (TB) have become important as structural compartments of molecular tweezers and compounds with high specific rotation. The formation of TB derivatives and byproducts from naphthalen-2-amine, methyl 6-aminonaphthalene-2-carboxylate, and anthracen-2-amine was studied. It was discovered that the formation of a naphthalenoide TB derivative is followed by the formation of a unique structural isomer of TB: spiroTB.

In 1887, Tröger published[1] a pure and simple isolation of a base character compound with summary formula $C_{17}H_{18}N_2$. The correct structure of Tröger's base (2,8-dimethyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine) was given by Spielman[2] as much as 48 years later, in 1935. Tröger's base (TB) became famous in 1944, when Prelog separated its enantiomers.[3] Since then, TB derivatives have become a touchstone of chiral separation performance and represent a textbook example of "chiral nitrogen". Another revival of TB derivatives came in the second half of the 20th century, when molecular engineers incorporated them into supramolecular systems, utilizing their chirality and rigid V shape. Today, several TB derivatives with unique properties are known and have become a phenomenon.[4]

Naphthalenoide TB derivatives are important due to their extremely high specific rotation[5] and their use as essential compartments of certain molecular tweezers.[6] However, only a few preparations are known; in addition, there is evidence that the formation of naphthalenoide TB derivatives is not

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(3) Prelog, V.; Wieland, P. *Helv. Chem. Acta* **1944**, *27*, 1127.
(4) (a) Vögtle, F. *Fascinating Molecules in Organic Chemistry*; Wiley: New York, 1992; Chapter 5, p 237. (b) Dolenský, B.; Elguero, J.; Král, V.; Pardo, C.; Valík, M. *Adv. Heterocycl. Chem.* **2007**, *93*, 1. (c) Sergeyev, S. *Helv. Chim. Acta* **2009**, *92*, 415.
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as unambiguous as that of benzenoide derivatives. For example, even though a preparation of TB derivative **1a** from naphthalen-2-amine was reported more than six times, some aspects remain unclear. Indeed, TB derivative **1a** was probably described by Reed[7] even a year before Tröger published his base, but with the incorrect summary formula $C_{24}H_{20}N_2$. This formula was corrected to $C_{23}H_{18}N_2$ and the structure related to a TB derivative by Morgan[8] in 1898. Both Reed and Morgan observed that formation of TB derivative **1a** is followed by that of acridine **2a**. Later, in 1964, Farrar reported[9] the formation of TB derivative **1a** together with two isomers with the same molecular formulas but different melting points. He explained their formation as a consequence of two reactive positions in naphthalen-2-amine. However, in 1998, Margitfalvi repeated Farrar's experiment and observed the formation of only one isomer represented by formula **1a**.[5] In contrast to Reed and Morgan, neither Farrar nor Margitfalvi reported the formation of acridine **2a**. In addition, Morgan reported another byproduct with summary formula $C_{22}H_{16}N_2$ (**3a**). Formation of **3a** was confirmed, and the structure suggested by Farrar (Figure 1);

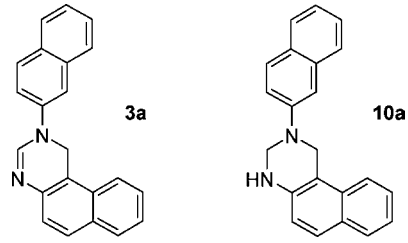


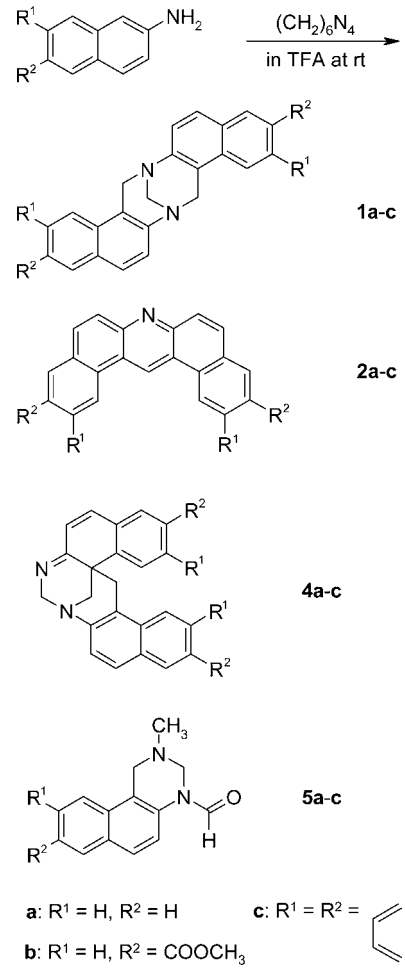
Figure 1. Quinazoline byproducts of Farrar's experiments.

however, it was not reported later by Margitfalvi. It is worth mentioning that dihydroquinazoline derivatives of **3a** are common products of treatment of arylamines with formaldehyde.[10]

This encouraged us to more deeply examine the preparation of some naphthalenoide TB derivatives. In connection to our research, we studied reactions of three naphthalenoide arylamines with HMTA in TFA: naphthalen-2-amine (series **a**), methyl 6-amino-naphthalene-2-carboxylate (series **b**), and anthracen-2-amine (series **c**). For comparison, we also performed a reaction with one non-naphthalenoide arylamine: 4-methoxyaniline (series **d**). In general, the treatment of naphthalenoide amines produces the expected TB derivatives **1** and acridines **2** but also produces spiroTB derivatives **4** and quinazolinecarbaldehydes **5** (Scheme 1); the yields are summarized in Table 1.

Except for anthracen-2-amine, we isolated known TB derivatives from the corresponding arylamines with good yields, i.e., **1a** (68%), **1b** (50%), and **1d** (69%). Although it

Scheme 1. Reaction of Naphthalenoide Arylamines with HMTA



is known[6,11] that *N*-alkylanthracen-2-amines give TB derivatives under these conditions, surprisingly, anthracen-2-amine itself gives no TB derivative **1c**. Thus, we used a treatment with aqueous CH_2O and HCl.[11] Although all of these amines have two reactive ortho positions, we found no evidence for the formation of any corresponding isomers of TB derivatives; i.e., we observed total regioselectivity.

Table 1. Preparative Yields of Studied Reactions

	preparative yields (%) from corresponding arylamines						
product	**a**[a]	**a**[d]	**b**[a]	**c**[a]	**c**[b]	**c**[c]	**d**[a]
1	68	72	50	0	61	0	69
2	2	3	5	3	24	38	0
3	0	2	0	0	0	0	0
4	4	2	20	0	6	0	0
5	8	0	22[e]	1	0	0	2
10	0	5	0	0	0	0	0

[a] HMTA, TFA, rt, 5 days. [b] Aqueous CH_2O, HCl, rt, 3 days. [c] Paraformaldehyde, TFA, 60 °C, 12 h, a complex mixture was formed. [d] Farrar's conditions,[9] aqueous CH_2O, HCl, 100 °C, 20 min. [e] not observed when conditions *c* are used.

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(7) (a) Reed, J. H. *J. Prakt. Chem.* **1886**, *34*, 160. (b) Reed, J. H. *J. Prakt. Chem.* **1887**, *35*, 298.
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(9) Farrar, W. V. *J. Appl. Chem.* **1964**, 389.
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In accordance with both Reed[7] and Morgan,[8] formation of TB derivatives **1a**−**c** was accompanied by that of acridines **2a**−**c**. We found no evidence (based on NMR) of acridine derivative formation from 4-methoxyaniline. Acridines **2a**−**c** are light yellow compounds with low solubility in organic solvents (e.g., benzene, chloroform, tetrahydrofuran, dimethyl sulfoxide), giving fluorescent light yellow solutions. Their solubility is significantly increased when TFA is used as a cosolvent, whereas in the case of **2c**, the solution turns from light yellow to dark red after addition of TFA. We recently reported acridine **2c** as an unidentified byproduct of TB **1c** preparation.[11]

The single-crystal X-ray diffraction of acridine **2c** revealed not only excellent packing via combination of CH−π and π−π interactions but also, surprisingly, helicity. The anthracene parts of **2c** are twisted; thus, their planes form an angle of about 16° (Figure 2). In other words, in the crystal,

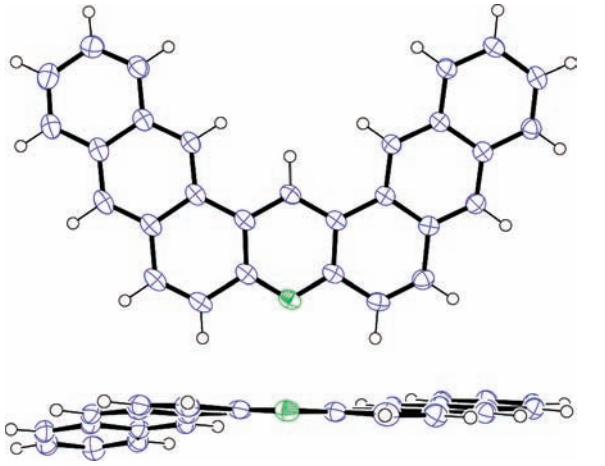
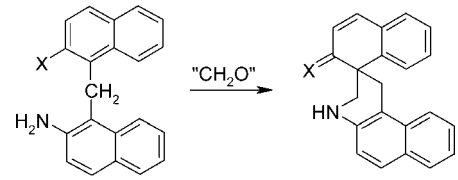


Figure 2. ORTEP representation of acridine **2c** (top and side view). Thermal ellipsoids are drawn at 50% probability level.

acridine **2c** is present as a mixture of two enantiomers differing in helicity. We tried to calculate an energy barrier between these enantiomers by quantum chemical calculations. We used the crystal structure geometry as a starting point for a B3LYP/6-31G** calculation. The optimized geometry was planar. We therefore presume that acridine **2c** exists as a planar (achiral) compound; however, its helical chirality can be induced and fixed.

The formation of acridines could be explained on the basis of a known reaction of naphthalen-2-amine with naphthalen-2-ol and a formaldehyde source, which generates compound **6** (Scheme 2).[12] In analogy, naphthalen-2-amine itself would give compound **7**, which is the general starting derivative for acridine preparations.[13] In addition, a similar system (1,1′-

Scheme 2. Possible Intermediates of Acridines **2** and SpiroTBs **4**



6 X = OH
7 X = NH_2

8 X = O
9 X = NH

binaphthalene-2,2′-diamines) was reported recently to form corresponding carbazole derivative spontaneously.[14]

Next, we found a formation of never-before-reported white crystalline compounds **4a**−**c**, which are well recognized by ^{1}H NMR spectroscopy via the AB system of the conjugated double bond (signals at 6.1−6.3 and 6.9−7.1 ppm). We found that **4a** is stable (80 °C, 16 h) in both TFA and concd aqueous HCl. The compounds **4** have the same summary formulas as the corresponding TB derivatives **1a**−**c**; moreover, similar to common TB derivatives, they contain a diazocine ring. Indeed, compounds **4** differ from common TB derivatives **1** by the connection of only one bond (C−C instead of C−N). Motivated also by the fact the structure of compounds **4** surprisingly contains a "spiro" carbon atom (originally aromatic), we suggested that these new derivatives should be named spiro Tröger's bases (spiroTB). The difference between spiroTB and TB can be shown by their overlay, which we demonstrate by superimposing[15] the naphthalene parts of spiroTB **4b** and TB **1a** crystal structures (Figure 3). It can be seen that the second "naphthalene" parts have opposing orientations.

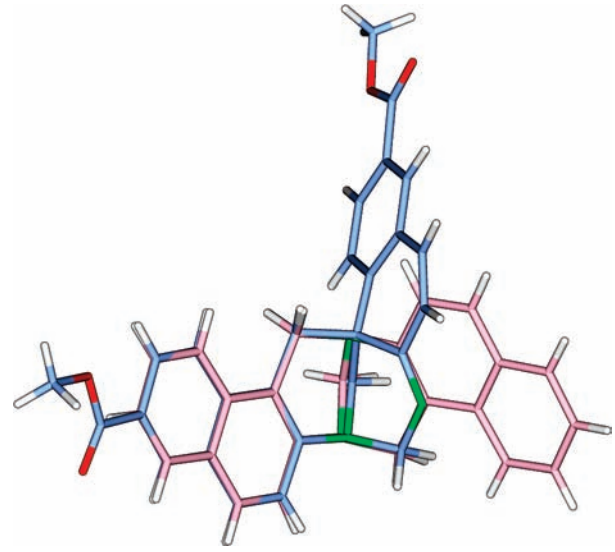


Figure 3. Overlay of spiroTB **4b** (blue) and TB **1a**[5] (pink) structures from single-crystal X-ray diffractions.

The formation of spiroTB **4** can be explained similarly to the formation of acridines **2** (vide supra). Möhrle reported

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that compound **6** reacts with paraformaldehyde to give spiro compound **8** (Scheme 2).[16] In analogy, naphthalen-2-amine itself would give compound **9**. It is obvious that two NH groups of compound **9** can be linked by the next formaldehyde molecule (when used in excess) to give corresponding spiroTB **4a**. In the case of 4-methoxyaniline, we did not observe the formation of corresponding spiroTB.

The last products that we isolated from the reactions of selected arylamines were quinazolinecarbaldehydes **5**. In contrast to acridines **2** and spiroTB **4**, the corresponding quinazolinecarbaldehyde **5d** is also formed in the case of 4-methoxyaniline (non-naphthalenoide arylamine). Compounds **5a**−**d** exist as a mixture of two isomers, which are recognizable in ^{1}H NMR (slow exchange).

Quinazolinecarbaldehydes **5** contain two nitrogen atoms, wherein one is obviously introduced from the starting arylamine; however, the second one probably originates from HMTA. This is supported by the formation of quinazolinecarbaldehydes **5** occurring only when HMTA is used as a source of formaldehyde (see Table 1). In addition, the presence of methyl and formyl groups on nitrogens of quinazolinecarbaldehydes **5** is surprising; however, N-methylated byproduct in TB preparations has been reported (HMTA was the formaldehyde source).[17] We presume that methyl and formyl groups originate from redox decomposition of HMTA; one CH_2–N group of HMTA is reduced to CH_3–N, while the second is oxidized to CH═N and subsequently hydrolyzed to the formyl group. We found no similar example of such decomposition in the literature.

Finally, for comparison, we also repeated Farrar's experiment[9] with naphthalen-2-amine (aqueous CH_2O, HCl, 100 °C, 20 min). We found the expected formation of TB derivative **1a**, acridine **2a**, and dihydroquinazoline **3a** but also spiroTB **4a** and tetrahydroquinazoline **10a** (Figure 1). This means that one of two TB isomers reported by Farrar could be spiroTB **4a**.

In conclusion, based on a limited series of arylamines, we found that naphthalenoide arylamine reacts with "formaldehyde" to generate the corresponding TB derivative **1**, which is followed, in contrast to the reaction of benzenoide arylamines, by the corresponding acridine **2** and TB isomer **4** (spiroTB). The formation of other byproducts like dihydroquinazoline **3**, quinazolinecarbaldehyde **5**, and tetrahydroquinazoline **10** depends on the formaldehyde source. Serendipitously, we found that helical chirality could be induced in dinaphthoacridine **2c**, which could be useful for chiral studies. For the first time, we report the structure of the TB isomer, spiroTB, which contains, similarly to common TB, a diazocine ring bridged by a methylene group. Thus spiroTB also has a rigid chiral structure, but against common TB, with the opposite space-arrangement of the naphthalene compartments. While one racemizable "chiral nitrogen" of common TB **1** is in spiroTB **4** superseded by a "chiral carbon", spiroTBs are expected to be more stable in acidic media. Lastly, if spiroTB **4a** is Farrar's TB isomer,[9] then there is another curious similarity between TB and spiroTB: Tröger's base had awaited accurate structural identification for 48 years and Farrar's TB isomer for 46 years—the future will show whether spiroTB receives as much attention as Tröger's base derivatives.

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Supporting Information Available: Experimental procedures, spectroscopic data for compounds **2a**−**c**, **3a**, **4a**−**c**, **5a**−**d** and **10a**, and CIF files of **2c** (CCDC 767173) and **4b** (CCDC 767174). This material is available free of charge via the Internet at http://pubs.acs.org.

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