

Communication

Methyl 8- and 5-Bromo-1,4-Benzodioxane-2-carboxylate: Unambiguous Identification of the Two Regioisomers

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Abstract: A variety of biological active compounds can be classified as 2-substituted 1,4-benzodioxanes bearing one or more substituents at the benzene. The synthesis of these important templates can be approached by different strategies. The most straightforward ones generally lead to mixtures of positional isomers, whose identification can be more problematic than separation. Here, we unambiguously elucidate, by HSQC and HMBC NMR analyses, the structure of methyl 8- and 5-bromo-1,4-benzodioxane-2-carboxylate, two versatile synthetic intermediates that are one-step-obtainable from commercial products and easily separable. As conceived, the identification procedure is, in principle, generalizable to any pair of 2-substituted 1,4-benzodioxanes bearing an X substituent at C(8) or C(5).

Keywords: 1,4-benzodioxane-2-carboxylate; HMBC NMR; regioisomers; structure elucidation



Citation: Armano, E.; Giraud, A.; Pallavicini, M.; Bolchi, C. Methyl 8- and 5-Bromo-1,4-Benzodioxane-2-carboxylate: Unambiguous Identification of the Two Regioisomers. *Molbank* **2023**, *2023*, M1623. <https://doi.org/10.3390/M1623>

Academic Editor: Ian R. Baxendale

Received: 9 March 2023

Revised: 8 April 2023

Accepted: 13 April 2023

Published: 18 April 2023



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1. Introduction

1,4-benzodioxane occurs as a key substructure in a variety of compounds, many of which exert biological activity and have therapeutic potential. Its applications in drug design, which range from antibacterial agents to cancer chemotherapies, adrenergic, serotonergic and nicotinic receptor antagonists and agonists, and a variety of enzyme inhibitors, have been recently reviewed [1]. Mostly, the interaction capabilities of these molecules with biological targets are critically related to two structural features, namely the substitution at the benzodioxane C(2) and the decoration of the benzene ring with different substitution patterns (Figure 1), the former resulting in chirality and often in high eudismic ratios [2] and the latter mainly translating into different selectivity profiles for receptor subtypes of the same family [2–4].

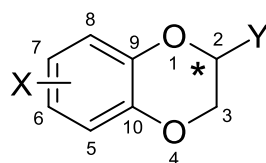
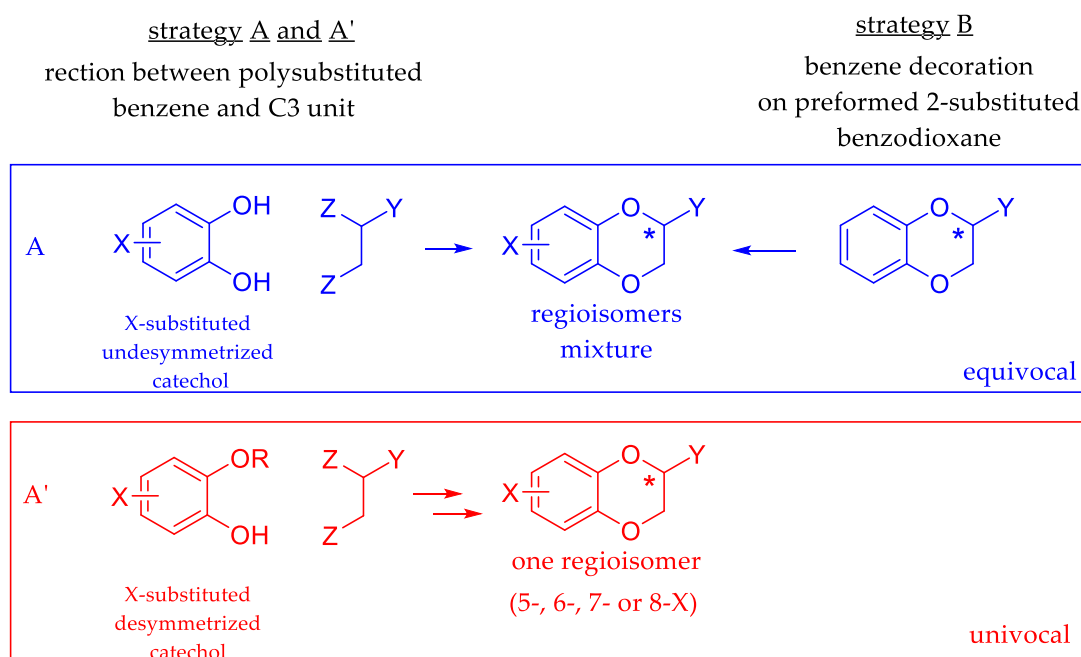


Figure 1. General formula of a chiral 2-substituted 1,4-benzodioxane bearing a substituent at the benzene ring.

Many methods, based on different approaches, have been developed to prepare both racemic and unichiral 2-substituted 1,4-benzodioxanes [5], while the decoration of the benzene ring of the latter relies on two alternative strategies: the construction of the bicycle by condensation of a C3 synthetic unit with benzene already bearing the desired substituents (strategies A and A', Scheme 1) or the benzene decoration of the preformed 2-substituted 1,4-benzodioxane (strategy B, Scheme 1) [6].



Scheme 1. Synthetic strategies to construct 2-substituted 1,4-benzodioxanes decorated at the benzene ring. Z: leaving EWG group in the nucleophilic attack by catechol; Y: any substituent, better if it makes carbon more electrophilic; R: removable O-protecting group.

Common issues of the two strategies are the production of positional isomers [6]. When applying the former approach, this problem can be bypassed by using differentially substituted desymmetrized catechols (strategy A'), such as *ortho*, *meta* and *para* substituted catechol monoethers, whose preparation and analytical characterization, however, is often laborious. A striking example is provided by the regioisomers of nitrocatechol monobenzyl ether [7], mono O-MEM-protected 4-bromocatechol [8] and 4-chlorocatechol monobenzyl ether [9], used to prepare 2-substituted 1,4-benzodioxane bearing -NO₂, -NH₂, -Br and -Cl substituents at the aromatic ring as nicotinic ligands [3,8] and antibacterial agents [9]. Otherwise, when using substituted undesymmetrized catechols (strategy A) or functionalizing preformed 2-substituted 1,4-benzodioxane at the benzene ring (strategy B), two or more positional isomers must be foreseen as products, whose unequivocal identification can be more difficult than their separation. Nevertheless, such synthetic approaches (strategies A and B) are attractive for a greater straightforwardness than strategy A'.

As we are interested in the preparation of 1,4-benzodioxane-based nicotinic ligands, here we report the unambiguous establishment of the 8- or 5-bromo substitution of methyl 1,4-benzodioxane-2-carboxylate, **1** and **2**, respectively, prepared according to approach A by HMBC NMR analyses (Figure 2). Among the polysubstituted benzodioxanes, we considered these two derivatives because of their versatility as synthetic intermediates, due to the exploitable reactivity of the ester function [6,10–12] and bromine [13,14], and their trivial accessibility by the reaction between commercially available methyl 2,3-dibromopropionate and 3-bromocatechol.

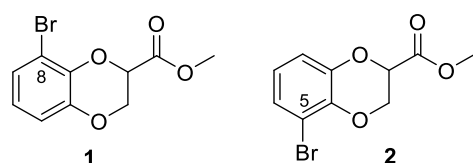


Figure 2. Methyl 8-bromo-1,4-benzodioxane-2-carboxylate (**1**) and methyl 5-bromo-1,4-benzodioxane-2-carboxylate (**2**).

2. Results and Discussion

Methyl 5-bromo- and 8-bromo-1,4-benzodioxane-2-carboxylate were easily prepared by a combination of equimolar amounts of commercially available methyl 2,3-dibromopropionate and 3-bromocatechol in acetone in the presence of three equivalents of potassium carbonate at reflux temperature overnight. After a standard work-up, the crude product was purified by chromatography on silica gel eluting with 80/20 petroleum ether/ethyl acetate isolating two fractions. The first eluted product, **1**, subsequently identified as methyl 8-bromo-1,4-benzodioxane-2-carboxylate by HMBC NMR analysis, was obtained with a 25% yield, while the second eluted product, **2**, subsequently identified as methyl 5-bromo-1,4-benzodioxane-2-carboxylate by HMBC NMR analysis, was obtained with a 40% yield.

As shown in Figure 3, ^1H NMR and ^{13}C NMR spectra of both **1** and **2** were consistent with the structure of methyl 1,4-benzodioxane-2-carboxylate brominated at C(5) or C(8), as expected on the basis of the used synthons. In the aliphatic region, two double doublets were imputable to the dioxane CH_2 and the triplet at the lower field to the dioxane CH , while, in the aromatic region, the triplet and the two double doublets, from the high field to low field, identified, respectively, the hydrogen *meta* to bromine and the two hydrogens *ortho* and *para* to bromine. However, the assignment of the **1** and **2** structures to the first and the second eluted products, respectively, or vice versa, was highly questionable because identical patterns of signals and multiplicity with non-decisive chemical shift differences were observed in the ^1H NMR spectra, while the ^{13}C NMR spectra were indistinguishable.

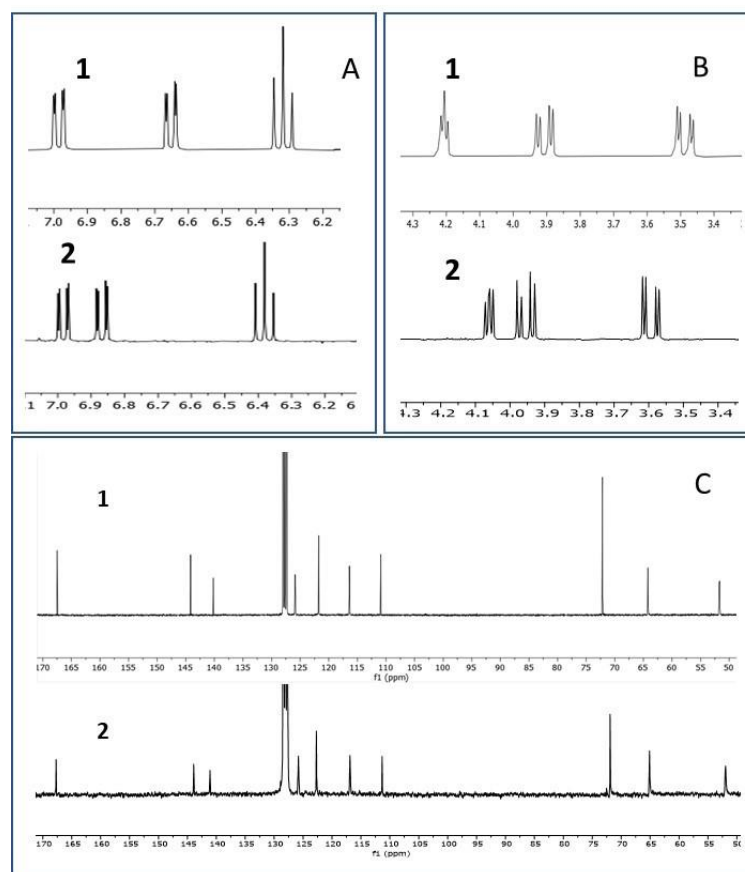


Figure 3. (A) Aromatic region and (B) aliphatic region of the ^1H NMR spectra of **1** and **2** and (C) ^{13}C NMR spectra of **1** and **2**. (A) The three adjacent hydrogens of the benzene ring give an analogous sequence of signals: dd, dd and t (from low field to high field). (B) The three hydrogens of the dioxane portion give an analogous sequence of three dd. (C) The spectra are indistinguishable. All the spectra were registered in C_6D_6 .

Additionally, HSQC NMR spectra were not conclusive. They allowed the certain assignment of four of the benzene carbons: (a) the signal at 111 ppm to the brominated carbon, (b) the signal at 122 ppm to the CH meta positioned to C-Br, (c) the signal at 126 ppm to the CH ortho positioned to C-Br, and, consequently, (d) the signal at 117 ppm to that para positioned to C-Br (Figure 3C). The distinctive assignments of the peaks at 140 and 144 ppm to the two quaternary carbons shared between the two cycles, namely (C(9) and C(10)), remained instead unresolved (Figure 3C). Therefore, we reasoned that HMBC NMR analysis could be resolute for the identification of the signals imputable to C(9) and C(10) and, consequently, for the unequivocal identification of the two regioisomers. In **1**, an important correlation with one or both methylene hydrogens of dioxane should identify C(10), with which the aromatic H giving a triplet should also be correlated (Figure 4). Otherwise, in **2**, we should observe an important correlation with one or both methylene hydrogens of dioxane by C(10) again, but no correlation or a weak one with the aromatic H giving the triplet (Figure 4). The latter, in **2**, should instead couple with C(9), in turn recognizable for no coupling with methylene hydrogens of dioxane. The two different patterns of three-bond C-H correlations, expected to distinguish **1** from **2**, are depicted in Figure 4.

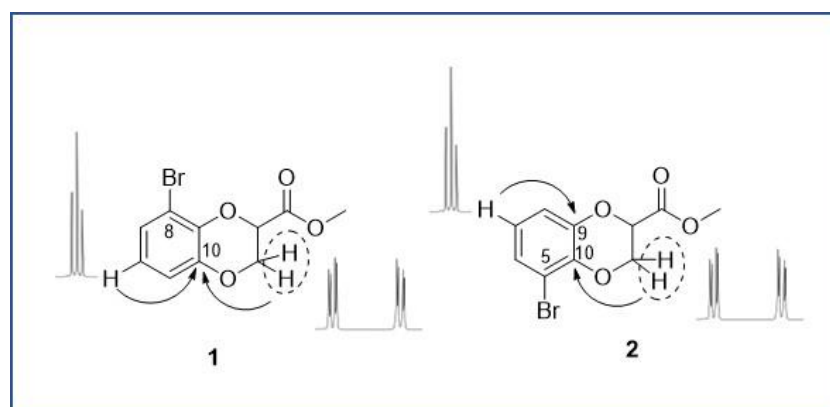


Figure 4. Expected important three-bond couplings of the dioxane geminal hydrogens with C(10) in both **1** and **2** and of the aromatic hydrogen giving a triplet with C(10) or C(9) in **1** and **2**.

Such expectations were confirmed by NMR experiments. In the HMBC spectrum of **1** (optimized for 8 Hz), both the aromatic proton meta positioned to bromine, unequivocally identified by triplet multiplicity, and the methylene protons of the dioxane ring, unequivocally identified by two double doublets, showed a strong $^3J_{H/C}$ correlation to carbon C(10) (Figure 5). In the HMBC spectrum of **2** (optimized for 8 Hz), one of the methylene protons of the dioxane ring showed a strong $^3J_{H/C}$ correlation to carbon C(10), as observed for **1**, but the aromatic proton meta positioned to bromine was correlated to carbon C(9) (Figure 6). These results unequivocally indicated that **1**, the first eluted product, was the isomer bearing bromine in the 8 position and that **2**, the second eluted product, was the 5-brominated isomer.

As a consequence of the identification by HMBC NMR, the difference in chemical shift of the proton *para* to bromine in the 1H NMR spectra (see Figure 3A) became diagnostic of the bromine position on the 1,4-benzodioxane nucleus: high-field H-5 in 8-brominated **1**, low-field H-8 in 5-brominated **2**.

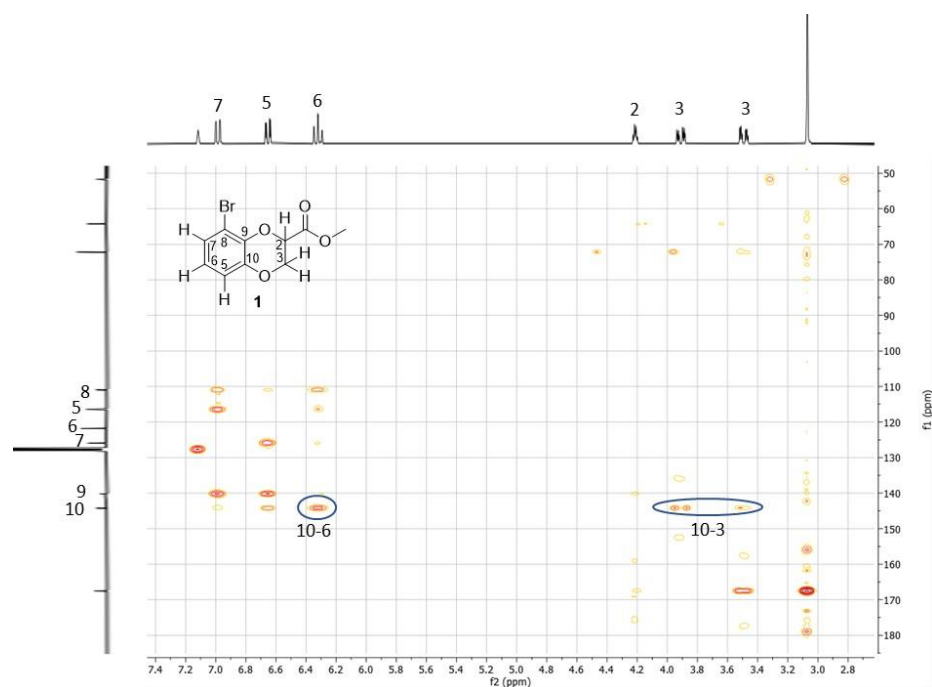


Figure 5. HMBC spectrum of **1** in C_6D_6 displaying important correlations between C(10) and H(6) and between C(10) and H(3).

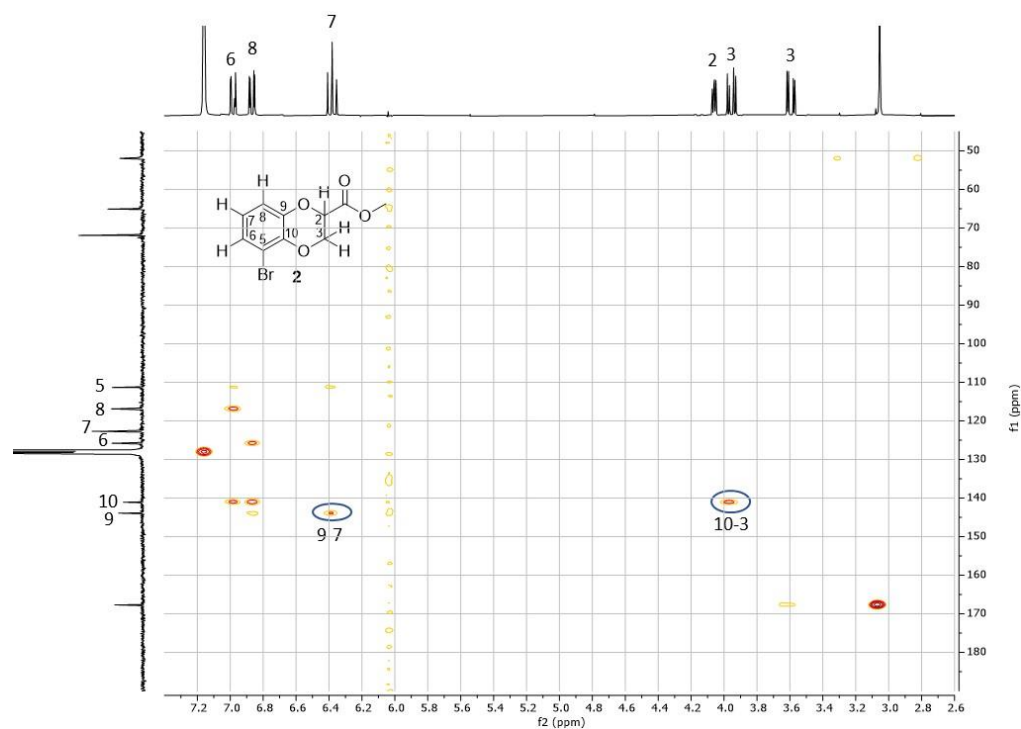


Figure 6. HMBC spectrum of **2** in C_6D_6 displaying important correlations between C(9) and H(7) and between C(10) and H(3).

3. Materials and Methods

The 1H and ^{13}C NMR and two-dimensional (2D) (HSQC, and HMBC) spectra, which are all reported as Supplementary Materials, were measured on a Varian Mercury 300 FT-NMR spectrometer operating at 300 MHz for 1H and 75 MHz for ^{13}C . NMR data were recorded at 25 °C, with chemical shifts δ reported in parts per million and coupling constants J in

Hertz. ^1H NMR spectra were recorded in C_6D_6 , while ^{13}C NMR, HSQC and HMBC spectra were recorded in C_6D_6 . Spectra can also be recorded in DMSO-d_6 .

4. Conclusions

In summary, we have unambiguously identified methyl 8-bromo- and 5-bromo-1,4-benzodioxane-2-carboxylate (**1** and **2**, respectively), two versatile synthons easily obtainable as a chromatographically resolvable mixture from 3-bromocatechol and methyl 2,3-dibromopropionate, by HMBC NMR. Structure elucidation was achieved by the unambiguous assignment of the two quaternary carbons shared between the two cycles in the HMBC spectrum of the two compounds and by a different pattern of $^3J_{\text{H/C}}$ correlation with these two carbons by the methylene hydrogens and the hydrogen *meta* to bromine. Since these latter hydrogens are unequivocally assignable in the ^1H NMR spectra, many other pairs of 2-substituted 1,4-benzodioxane bearing an X substituent at the 8 or 5 position may be unambiguously identified by the same comparison of $^3J_{\text{H/C}}$ data that we have here applied to the regioisomers **1** and **2**.

Supplementary Materials: The following supporting information can be downloaded online, Preparation of **1** and **2**; ^1H NMR spectra of **1** and **2** in C_6D_6 ; ^{13}C NMR spectra of **1** and **2** in C_6D_6 ; HSQC spectra of **1** and **2** in C_6D_6 ; HMBC spectra of **1** and **2** in C_6D_6 .

Author Contributions: Conceptualization, C.B.; methodology, E.A.; investigation, E.A. and A.G.; writing—review and editing, M.P.; supervision, C.B. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Data Availability Statement: The data for the compound presented in this study are available in the Supplementary Materials of this article.

Acknowledgments: The authors acknowledge support from University of Milan through the APC initiative.

Conflicts of Interest: The authors declare no conflict of interest.

Sample Availability: Samples of the compounds are not available from the authors.

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