Short Note

2,6-Dimethoxybenzyl Bromide

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Abstract: The unstable title compound has been characterized for the first time. Its melting point, UV, IR, ^{1}H and ^{13}C-NMR and high-resolution mass spectra are presented. The X-ray structure has also been determined and shows a rather long C–Br bond perpendicular to the otherwise planar molecule.

Keywords: 2,6-dimethoxybenzyl bromide; X-ray structure; NMR spectra; IR spectrum; UV spectrum

1. Introduction

In the course of the synthesis of a natural product, we recently required 2,6-dimethoxy benzyl bromide **1** and were surprised to find that this simple aromatic compound has apparently not been characterised in any way before. The first mention of the compound in the literature seems to be in 1988, when it was briefly evaluated together with other methoxybenzyl bromides as a selective OH-protecting reagent in carbohydrate chemistry [1]. Since then, it has found increasing use both for this application [2,3], and in construction of new ligands [4], organocatalysts [5], antibacterial agents [6], synthetic intermediates [7], insecticides [8] and anticancer agents [9]. However, in all these cases, it is prepared and used immediately without any attempt at isolation or characterisation. The method of preparation is most commonly by reaction of the corresponding alcohol **2** with phosphorus tribromide [6], although treatment of **2** with hydrobromic acid [8], and radical bromination of 2,6-dimethoxytoluene **3** with *N*-bromosuccinimide [2] have also been used (Scheme 1).
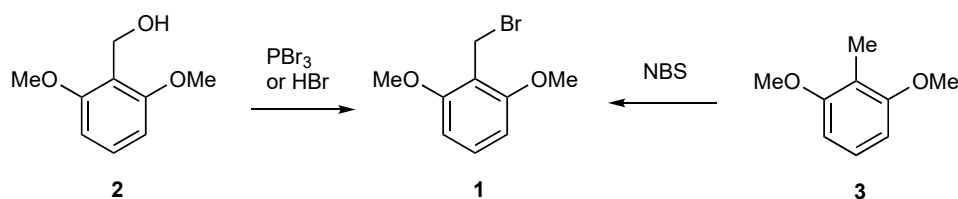
Scheme 1. Synthetic routes to compound **1**.

This situation is in marked contrast to most of the other isomeric dimethoxybenzyl bromides (Figure 1), where both the 2,3-isomer **4** [10] and the 3,4-isomer **5** [11,12] have been known since the 1920s and have been thoroughly characterised using all the main analytical and spectroscopic methods. The 2,5-isomer **6** was first reported in 1953 [13] and full spectra were subsequently described [14]. The 3,5-isomer **7** was first prepared in 1962 [15] and is the only one of the six isomers to be characterised by X-ray diffraction to date, with both powder [16] and single crystal [17] data available. Interestingly, the 2,4-isomer **8** has a similar lack of characterisation to **1**, being mentioned in two patents [18,19] as being generated from the corresponding alcohol and PBr$_3$ and used immediately without isolation, and in terms of data, only the ^{1}H-NMR chemical shift for its CH$_2$ is available [20].

**Figure 1.** The other isomeric dimethoxybenzyl bromides.

We here describe the preparation, isolation and full characterisation of compound **1** including its melting point, UV, IR, ^{1}H and ^{13}C-NMR spectra, HRMS and X-ray structure determination. Some observations on the stability and decomposition of this reactive compound are also documented.

2. Results

Reaction of 2,6-dimethoxybenzyl alcohol, prepared by esterification then LiAlH$_4$ reduction of commercially available 2,6-dimethoxybenzoic acid [21], with 0.33 equivalents of PBr$_3$ in diethyl ether at 0 °C, followed by aqueous work-up, drying of the ether extract and evaporation gave the target compound **1** as colourless crystals, mp 65–67 °C. However, it was quickly discovered that the compound decomposed over a period of hours to days at room temperature to give a dark purple polymeric material, insoluble in any common solvents. The decomposition seemed to be accelerated by light, heat or contact with a nickel spatula and, once initiated, seemed to be autocatalytic so that, once it started, it accelerated rapidly. Despite this, samples of the compound have been stored in a foil-covered flask in a refrigerator at 5 °C for several months without decomposition.

The UV, IR and ^{1}H and ^{13}C-NMR spectra could be recorded by working rapidly and with suitable precautions, and the data documented in the Experimental Section and illustrated in the Supplementary Material are in agreement with expectation and also with those for the isomeric compounds of Figure 1. In particular, the UV spectrum consisted of a series of three shoulders at 291, 278 and 246 nm of steadily increasing intensity, while the most prominent peak in the IR spectrum was at 1088 cm^{-1}, attributable to aromatic C–Br stretch. The NMR spectra showed the expected shielding effect of OMe with 3/5 positions giving signals at δ_H 6.54 and δ_C 103.7, respectively. The quaternary carbon at C-1 gave a particularly weak signal at δ_C 114.4 ppm. High-resolution mass spectrometry gave a signal at *m/z* 151, corresponding to M$^+$–Br and showing good agreement with the theoretical value. This gives some hint as to the mechanism of decomposition since the carbocation **9** formed by ionisation with loss of Br$^-$ is significantly stabilised by the two OMe groups (Scheme 2), and we speculate that the main mode of decomposition may be bromide mediated *O*-demethylation of **9** to give the *ortho*-quinomethane species **10,** which then polymerises.
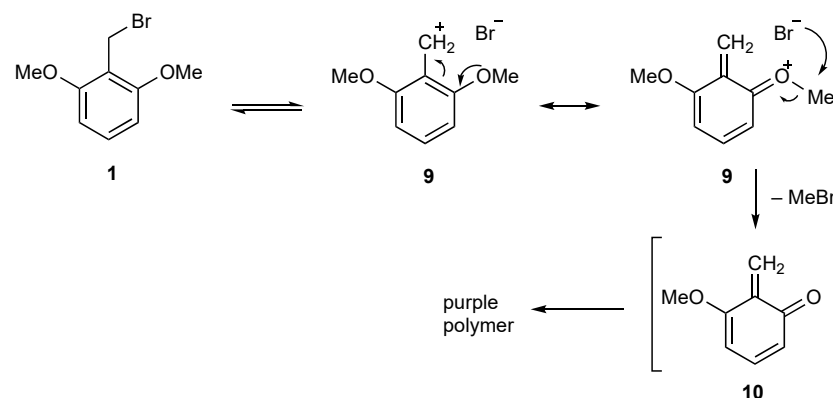
Scheme 2. Suggested mode of decomposition for **1**.

Crystals suitable for X-ray diffraction were obtained directly from the freshly prepared material and quickly mounted while still cold for data collection at 93 K. The resulting molecular structure (Figure 2) shows the two methoxy groups as essentially coplanar with the benzene ring while the CH_2–Br bond is essentially orthogonal to it. The arrangement of the four molecules in the unit cell is also shown in Figure 2.
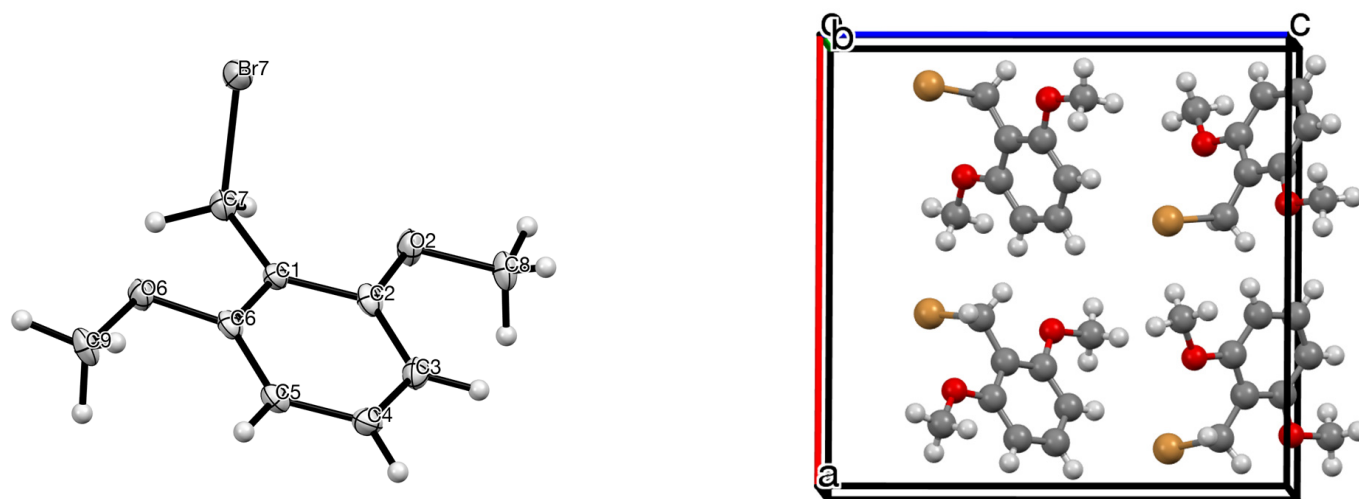
Figure 2. (**left**) Molecular structure of **1** with anisotropic displacement ellipsoids drawn at 50% probability level and showing numbering system used. (**right**) View of unit cell along the b axis showing packing.

A good number of similar compounds have been crystallographically characterised and a comparison of the key parameters for the Ar–CH_2–Br group for a selection of these (Figure 3) is presented in Table 1. As compared to the unsubstituted benzyl bromide **9** compound **1** shows lengthening of both ring–CH_2 and CH_2–Br bonds and a torsion angle much closer to 90°. In considering the data for the isomeric 3,5-dimethoxy compound **7,** it should be noted that the first set of data [16] is derived from a powder diffraction study, and the discrepancy between this and the single-crystal data [17], as well as all the other values in Table 1, is likely to be due to systematic errors linked to the different technique. The situation for the apparently good model compound **10** is complicated by the fact that there are two separate crystal forms containing, respectively, three and two independent molecules in the unit cell and each molecule has all three CH_2Br groups non-equivalent, thus delivering a total of 15 values for each parameter, which actually span the full range of values exhibited by the other compounds in the Table. Nonetheless, it can be seen that the parameters listed for **1** are broadly in line with those of closely similar compounds. but the CH_2–Br bond length is among the longest and the ring–CH_2–Br torsion angle is among the closest to 90°.

In summary, the simple but unstable compound 2,6-dimethoxybenzyl bromide has been characterised for the first time, with its melting point, UV, IR, ^{1}H and ^{13}C-NMR spectra recorded. A correct HRMS measurement was obtained for M$^+$–Br. The X-ray structure was also determined and shows structural parameters in good agreement with similar highly substituted benzyl bromides.
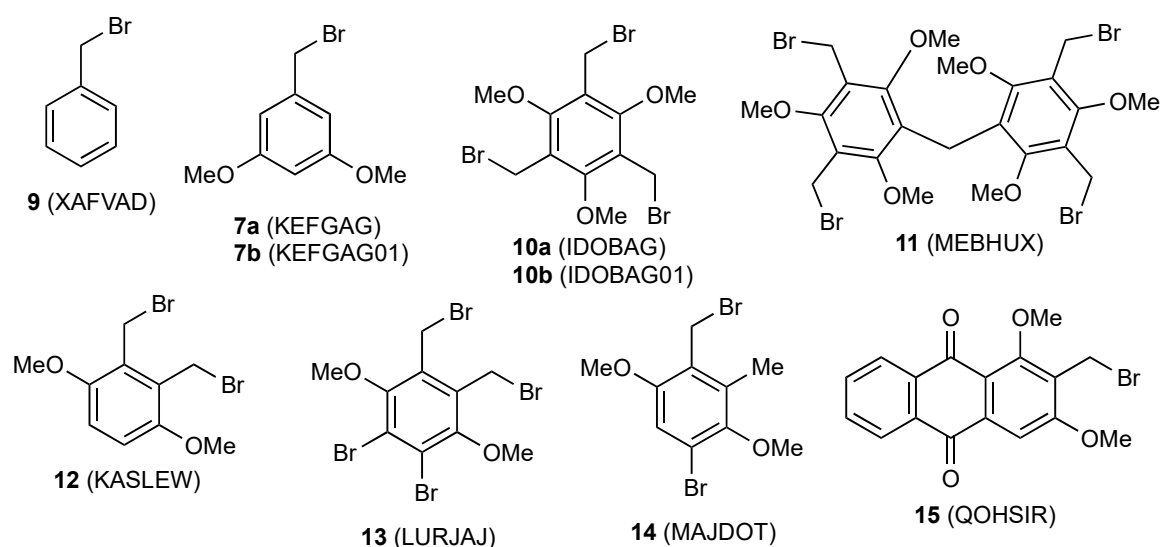
Figure 3. Comparison crystal structures with CSD reference codes.

Table 1. Geometric parameters for **1** and other comparable benzyl bromides.

Compd	Length C–CH$_2$ (Å)	Length CH$_2$–Br (Å)	Angle C–CH$_2$–Br °	Torsion Angle Ring/CH$_2$–Br °	Ref
1	1.488 (6)	1.992 (4)	112.4 (3)	88.67	this work
9	1.465 (14)	1.971 (11)	110.3 (6)	77.07	[22]
7a [a]	1.466 (2)	1.908 (1)	116.68 (8)	75.65	[16]
7b	1.498 (4)	1.987 (3)	110.8 (2)	75.82	[17]
10a [b]	1.475 (4)–1.491 (5)	1.964 (4)–1.980 (2)	111.2 (2)–113.4 (2)	78.57–89.93	[23]
10b [c]	1.485 (4)–1.498 (6)	1.972 (4)–1.988 (3)	110.7 (2)–114.2 (2)	76.64–89.86	[24]
11	1.495 (3)	1.979 (3)	111.6 (2)	89.38	[25]
	1.491 (3)	1.984 (2)	113.1 (2)	83.19	
12	1.491 (3)	1.987 (2)	112.0 (1)	83.43	[26]
	1.493 (2)	1.978 (2)	111.2 (1)	79.42	
13	1.49 (1)	1.947 (8)	111.4 (5)	81.47	[27]
	1.50 (1)	1.965 (8)	110.4 (5)	84.45	
14	1.49 (1)	1.991 (7)	112.3 (5)	82.45	[28]
15	1.497 (4)	1.975 (3)	110.1 (2)	78.99	[29]

[a] powder diffraction; [b] range of 9 values; [c] range of 6 values.

3. Experimental Section

Melting points were recorded on a Reichert hot-stage microscope (Reichert, Vienna, Austria) and are uncorrected. UV spectra were recorded using a Shimadzu (Milton Keynes, UK) instrument and IR spectra were recorded on a Perkin-Elmer 1420 instrument (Perkin-Elmer, Waltham, MA, USA). NMR spectra were recorded using a Bruker (Bruker, Billerica, MA, USA) AV instrument at 300 MHz (^{1}H) and a Bruker AV III instrument at 125.8 MHz (^{13}C) in CDCl$_3$ with chemical shifts given with respect to Me$_4$Si and coupling constants in Hz. HRMS was recorded using a Thermo Fisher Exactive Orbitrap instrument in ESI mode.

*2,6-Dimethoxybenzyl Bromide (**1**)*

A solution of 2,6-dimethoxybenzyl alcohol [21] (1.0 g, 6.53 mmol) in dry diethyl ether (20 mL) was stirred at 0 °C while PBr$_3$ (0.21 mL, 2.18 mmol) was added dropwise. After stirring for 1 h, methanol (2 mL) was added, followed by water (20 mL). The organic later was separated and the aqueous layer extracted with Et$_2$O (20 mL). The combined organic extracts were dried (MgSO$_4$) and evaporated under reduced pressure to give the product (1.32 g, 87%) as colourless crystals, mp 65–67 °C, which were stored at 5 °C in the dark; UV/Vis (MeCN): λ$_{max}$ (log ε) 291 (3.39), 278 (3.50), 246 (3.86) nm; IR (ATR): 3273, 1734,

1593, 1474, 1433, 1258, 1150, 1107, 1088, 1032, 781, 735, 590, 523 cm^{-1}; ^{1}H-NMR (300 MHz, CDCl$_3$): 7.24 (1H, t, *J* = 8.4 Hz, 4-CH), 6.54 (2H, d, *J* = 8.4 Hz, 3,5-H), 4.70 (2H, s, CH$_2$Br), 3.89 (6H, s, 2 OCH$_3$); ^{13}C-NMR (126 MHz, CDCl$_3$): 158.5 (2C, C-2,6), 130.1 (CH, C-4), 114.4 (C, C-1), 103.7 (2CH, C-3,5), 55.9 (2 OCH$_3$), 23.7 (CH$_2$); HRMS (ESI): Calcd. for C$_9$H$_{11}$O$_2$ (M–Br): 151.0759. Found: 151.0752.

The structure was determined on a Rigaku XtaLAB 200 diffractometer using graphite monochromated Mo Kα radiation λ = 0.71075 Å.

Crystal data for C$_9$H$_{11}$BrO$_2$, *M* = 231.09 g mol^{-1}, colourless prism, crystal dimensions 0.18 × 0.10 × 0.02 mm, orthorhombic, space group Pna2$_1$ (No. 33), *a* = 13.297 (8), *b* = 5.033 (3), *c* = 13.789 (9) Å, α = β = γ = 90.00°, *V* = 922.8 (10) Å^3, *Z* = 4, D_{calc} = 1.663 g cm^{-3}, *T* = 93 K, *R*1 = 0.0269, *Rw*2 = 0.0654 for 1554 reflections with *I* > 2σ (*I*), and 111 variables, R$_{int}$ 0.0537, goodness of fit on F^2 1.084. Data have been deposited at the Cambridge Crystallographic Data Centre as CCDC 2097451. The data can be obtained free of charge from the Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/getstructures. The structure was solved by direct methods and refined by full-matrix least-squares against F^2 (SHELXL Version 2018/3 [30]).

Supplementary Materials: The following are available online, Figure S1: UV spectrum of **1**; Figure S2: IR spectrum of **1**; Figure S3: ^{1}H-NMR spectrum of **1**; Figure S4: ^{13}C-NMR spectrum of **1**; Figure S5: HRMS measurement on **1**.

Author Contributions: E.A.S. prepared the compound and obtained the NMR spectra; A.M.Z.S. collected the X-ray data and solved the structure; R.A.A. designed the experiments, ran the IR and UV spectra, analysed the data, and wrote the paper. All authors have read and agreed to the published version of the manuscript.

Data Availability Statement: The X-ray data is deposited at CCDC as stated above and all spectroscopic data is in the Supplementary Material.

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

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