

## Bromination of 2,5-dimethoxybenzaldehyde

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### RINGKASAN

Pengbrominan terhadap 2,5-dimetoksibenzaldehyd (1) menghasilkan 4-bromo-2,5-dimetoksibenzaldehyd (2) dan bukan 6-bromo-2,5-dimetoksibenzaldehyd (3) seperti yang dilaporkan oleh Rubenstein (1925). Hasil percubaan menunjukkan bahawa kunjugasi kumpulan karbonil dengan kumpulan metoksi pada kedudukan orto (seperti struktur 4) berkemungkinan tidak menentukan orientasi tindak balas pengbrominan ini. Satu siri tindak balas yang mengesahkan struktur hasil tindak balas pengbrominan tersebut akan dibincangkan.

### SUMMARY

Bromination of 2,5-dimethoxybenzaldehyde (1) gives 4-bromo-2,5-dimethoxybenzaldehyde (2) and not 6-bromo-2,5-dimethoxybenzaldehyde (3) as previously reported by Rubenstein (1925). It appears that the conjugation of the carbonyl group with the ortho methoxy group (as structure 4) does not control the orientation of this bromination reaction. A series of reactions which confirm the structure of the bromination product will be discussed.

### INTRODUCTION

Rubenstein (1925) reported that bromination of 2,5-dimethoxybenzaldehyde (1) using bromine in acetic acid at room temperature gave only 6-bromo isomer (3). He reached this conclusion by analogy with the nitration of 2,5-dimethoxybenzaldehyde (1) which gives mainly 6-nitro isomer (5) and only 20% of the 4-nitro isomer (6). These nitration products are consistent with the stabilisation of the intermediate cation, involving conjugation of the substituents with the ortho methoxy group via the canonical structure (4) (Howe, C.A. *et al.*, 1965). Conjugation of these groups tend to isolate their effect from the rest of the ring system and therefore the site of attack is determined by the remaining methoxy group: thus the 6-isomer (5) is favoured. He then oxidised the bromination product to the corresponding acid which had m.p. 164-165°C.

### EXPERIMENT

The n.m.r. spectra, was quoted in p.p.m. internal tetramethylsilane, and was recorded at 60MHz, (Perkin Elmer R12A and R12B instruments). Melting point determinations were uncorrected.

#### *4-Bromo-2,5-dimethoxybenzaldehyde (2)*

To a cooled stirred solution (ice-water bath) of 2,5-dimethoxybenzaldehyde (1) (1.7g) in glacial acetic acid (9 ml) was added bromine in glacial acetic acid (9 ml). The reaction mixture was covered with aluminium foil to exclude light. After stirring for 4 hours at room temperature, the brown solution was poured into water. The white precipitate was filtered off, washed with water and dried. The pure product (2) was obtained by crystallisation from ethanol as yellow needles, m.p. 131-132°C, (Bortnik, S.P. *et al.*, 1972) Bromination using bromine

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in a mixture of sulfuric acid and acetic acid, and bromine in chloroform was carried out by using the standard method.

#### 4-Bromo-2,5-dimethoxytoluene (7)

A mixture of 4-bromo-2,5-dimethoxybenzaldehyde (2) (230 mg), hydrazine hydrate (5.0 ml, 98%) and potassium hydroxide (6 pellets) in diethylene glycol (16 ml) was heated gradually until the mixture refluxed at 130°C. After 1 hour the condenser was removed and the reaction mixture was heated gradually until the temperature reached 150°C. It was then refluxed at this temperature for an additional 1.5 hours and subsequently cooled to room temperature, diluted with water, extracted with ether, washed with water and dried over CaCl<sub>2</sub>. After removing the solvent, the product was sublimed to give a white solid (7) (110 mg), m.p. 87-88°C (Luttringhaus, A. *et al.*, 1942) 91°C.

4-Bromo-2,5-dimethoxytoluene (7) was also prepared by bromination of 2,5-dimethoxytoluene (8) using bromine in chloroform by the standard method. The product had m.p. 87-87.5°C; undepressed on admixture with material prepared by reduction of 4-bromo-2,5-dimethoxybenzaldehyde (2) as described above.

#### 2,5-Dimethoxytoluene (8)

This compound was prepared by reduction of 2,5-dimethoxybenzaldehyde (1) using normal Wolff-Kishner reduction in 60% yield: as a colourless oil, it had  $\delta$ (CDCl<sub>3</sub>) 6.69(3H, s, Ar-H), 3.75(3H, s, OMe), 3.72(3H, s, OMe) and 2.20(3H, s, Me).

## RESULTS AND DISCUSSION

Bromination of 2,5-dimethoxybenzaldehyde (1) was initially carried out using bromine in acetic acid as described by Rubenstein (1925). Recrystallising the product from ethanol, gave a white solid, m.p. 131-132°C., in contrast to Rubenstein who reported his compound to melt at 125-132°C. This product was shown to be 4-bromo-2,5-dimethoxybenzaldehyde (2) by its n.m.r. spectrum in d-chloroform as well as in d<sub>6</sub>-benzene. Its n.m.r. in d-chloroform showed a singlet at  $\delta$ 10.1 due to the formyl group, two singlets at  $\delta$ 7.32 and 7.24 due to the two aromatic protons para to each other, and a singlet at  $\delta$ 3.88 due to the two methoxy groups. Its n.m.r. spectrum in d<sub>6</sub>-benzene showed a singlet at  $\delta$ 10.39 due to formyl group, two singlets at  $\delta$ 6.81 and 6.85 due to the two aromatic protons,

and two singlets at  $\delta$ 3.19 and 2.98 due to the two methoxy groups. An AB quartet would have been expected for the two aromatic protons of the 6-bromo compound (3).

The same results were obtained by repeating the bromination reaction using bromine in a mixture of sulfuric acid and acetic acid, and bromine in chloroform.

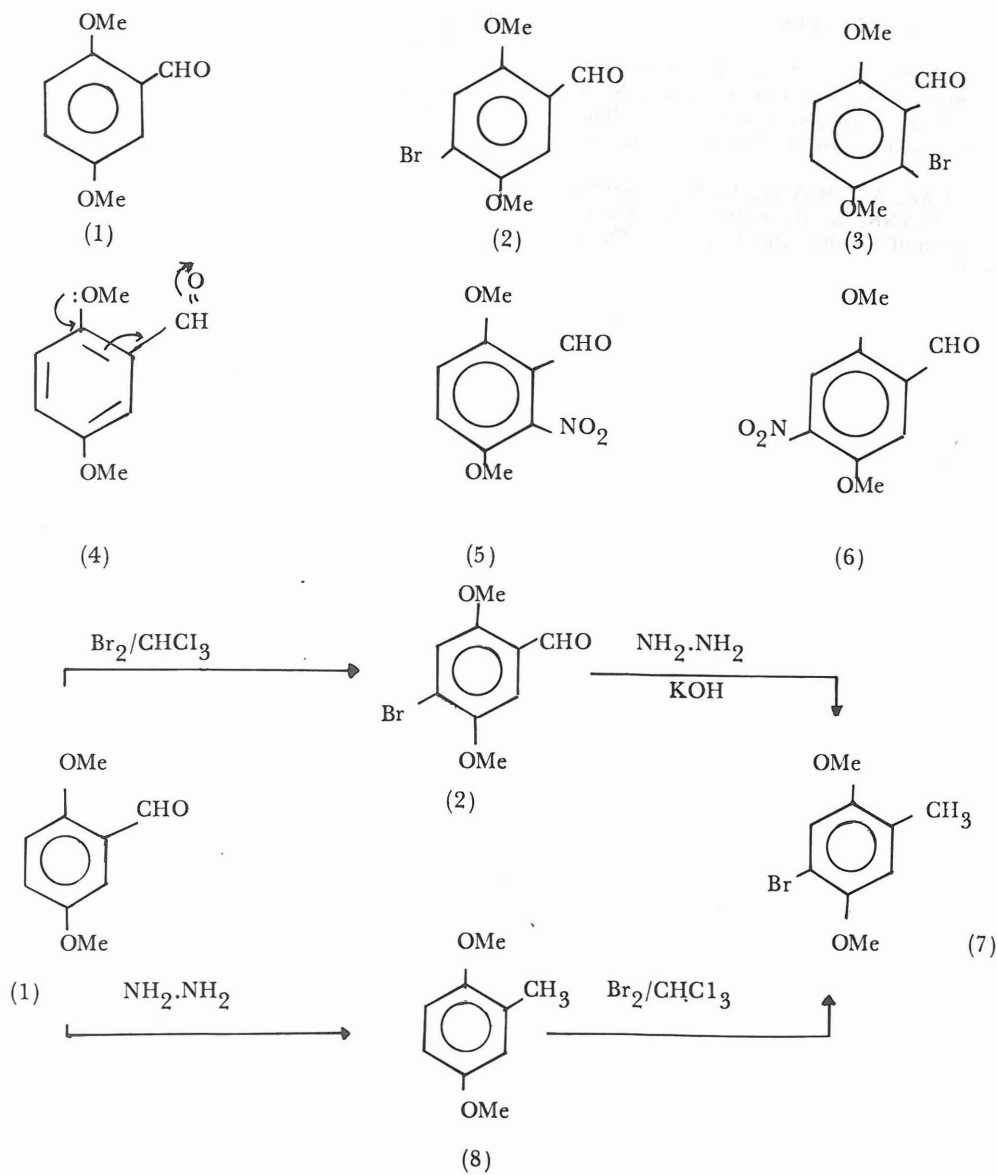
A series of reactions (Scheme 1) was also investigated in order to confirm the structure of the bromination product. The product was initially reduced to the corresponding 4-bromo-2,5-dimethoxytoluene (7) by the normal Wolff-Kishner reduction process at 150°C. This reduction gave a white solid, m.p. 87-88°C. Its n.m.r. spectrum in d-chloroform showed two singlets at  $\delta$ 6.98 and 6.73 due to the two aromatic protons para to each other, and two singlets at  $\delta$ 3.80 and 3.75 due to the methoxy group, and a singlet at  $\delta$ 2.18 due to the methyl group.

The bromo compound (7) was also prepared by a different method. Wolff-Kishner reduction of 2,5-dimethoxybenzaldehyde (1) gave 2,5-dimethoxytoluene (8), which was then brominated with bromine in chloroform to give the bromo compound (7) as the only product. This compound was found to be identical (mix. m.p.) with the reduction product of the compound obtained by bromination of 2,5-dimethoxybenzaldehyde (1). These results confirm that the bromination of 2,5-dimethoxybenzaldehyde (1) gives the 4-bromo isomer (2) and not 6-bromo isomer (3).

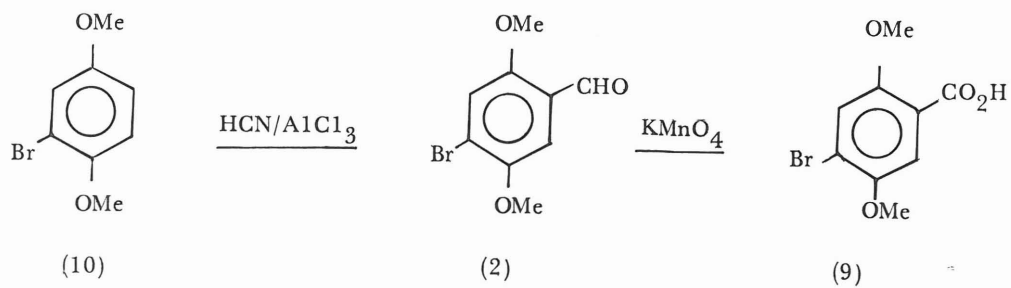
Bortnik *et al.* (1972), also proved that Rubenstein's result must be in error. They prepared 4-bromo-2,5-dimethoxybenzoic acid (9) from 2,5-dimethoxybromobenzene (10) as shown in Scheme 2, and found it had m.p. 164-165°; identical (m.p.) with the compound previously reported by Rubenstein.

Since bromination of 2,5-dimethoxybenzaldehyde (1) using bromine in a mixture of sulfuric acid and acetic acid, bromine in acetic acid, and bromine in chloroform, all give 4-bromo isomer (2), it appears that the brominating species in this bromination reaction is probably just the bromine molecule, which is polarised by the ring system. Evidence for the bromine molecule as the attacking species is that in some cases of bromination of the aromatic system, the presence of acid, base or other ions accelerate the reactions. (March, J. 1979).

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Scheme 1



Scheme 2

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