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ANISE OIL AS PRECURSOR FOR PHENYLETHYLAMINE DESIGNER DRUGS OF THE 2C-X FAMILY

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INTRODUCTION:

Anethole is the main component of anise oil and can be used in the (clandestine) synthesis of 4-methoxy(meth)amphetamine (PM(M)A). It has now been found that anethole can be used as precursor for other phenylethylamines (PEAs) as well. The finding is exemplified for 4-bromo-2,5-dimethoxyphenylethylamine (2C-B)

FIGURE 1 : Anethole is oxidized to anisaldehyde **(A)**, which after isolation is subjected to a Baeyer-Villiger oxidation reaction with performic or peracetic acid **(B)**. The O-formyl-4-methoxyphenol obtained this way is hydrolyzed **(C)**. 4-Methoxyphenol is subsequently formylated using the Reimer-Tiemann method **(D)** and the obtained 2-hydroxy-5-methoxybenzaldehyde is methylated with dimethylsulfate to 2,5-dimethoxybenzaldehyde **(E)**.
The mass spectra of 2-hydroxy-5-methoxybenzaldehyde and 2,5-dimethoxybenzaldehyde are shown.

INSTRUMENTATION:

GC/MS analysis by Agilent 6890 Plus GC coupled to Agilent 5973N MSD:
- column: VF-5MS factorFour (30 m x 0.250 mm x 0.25 µm);
  carrier gas: He, flow rate of 1 mL/min.
- oven programming: 50°C (1 min), 35°C/min to 100°C, 10°C/min to 270° (20 min).
- MSD: EI mode (70 eV), 36-500 amu, 4.00 min solvent delay.

SYNTHESIS:

SYNTHESIS OF 2,5-DIMETHOXYBENZALDEHYDE (FIG. 1)

A : Anisaldehyde from anethole via oxidative cleavage: 20 g anise oil was suspended in a mixture of 150 mL water and 30 mL conc. sulfuric acid; addition of 55 g sodium bichromate at such a rate that the temperature did not exceed 40°C. The reaction mixture was extracted with 4 x 125 mL toluene and the solvent evaporated. The residual oil was vacuum distilled to yield 9.1 g anisaldehyde.

B : O-formyl-4-methoxyphenol: 6 mL anisaldehyde was dissolved in 75 mL dichloromethane (DCM). A mixture of 12 g hydrogen peroxide and 10 mL conc. formic acid was added over 30 min. The reaction mixture was gently refluxed for 21 h.

C : 4-methoxyphenol: Evaporating the solvent from reaction mixture **B** and taking up the residue in 100 mL aqueous NaOH (20%) (25 mL MeOH as co-solvent) yielded 4.1 g 4-methoxyphenol as a white crystalline product after the usual work-up and purification steps.

D : Reimer-Tiemann formylation of 4-methoxyphenol: 124.1 g 4-methoxyphenol was dissolved in NaOH solution (320 g NaOH in 400 mL water). In total, 161 mL chloroform was added. The usual work-up and steam distillation yielded 109.8 g of a clear yellow oil that did not solidify upon standing at room temperature (GC/MS: 94% 2-hydroxy-5-methoxybenzaldehyde).

E : Methylation of 2-hydroxy-5-methoxybenzaldehyde: The yellow oil from **D** was used without further purification. A 250 mL RB flask was charged with 100 mL acetone, 14 g anhydrous potassium carbonate and 10 g 2-hydroxy-5-methoxybenzaldehyde; the mixture was brought at reflux temperature and 11 g dimethyl sulfate was added. The reaction was continued for 4 hours. The solvent is evaporated and the crude end product crystallized in cold water. Recrystallization from EtOH/water yielded 8.3 g 2,5-dimethoxybenzaldehyde (GC/MS: 98%+ 2,5-dimethoxybenzaldehyde)

SYNTHESIS OF 4-BROMO-2,5-DIMETHOXYPHENYLETHYLAMINE (FIG. 2)

A 250 mL RB flask was charged with 16.6 g 2,5-dimethoxybenzaldehyde, 1.6 g NaOAc and 50 mL nitromethane. Refluxing for 4h yielded 14.4 g of the corresponding nitrostyrene [1] after recrystallization.
5.0 g of 2,5-dimethoxylphenyl-2-nitroethene was added to a solution of 4.0 g sodium borohydride in 100 mL isopropanol. This yielded 4.2 g of a yellow oil after decomposition of the excess borohydride followed by the usual work-up (B).
The 2,5-dimethoxyphenyl-2-nitroethane was dissolved in 100 mL isopropanol with 8 molar equivalents Zn and 3.5 molar equivalents HOAc (relative to amount of Zn). This yielded 2.0 g of 2,5-dimethoxyphenylethylamine as a faintly yellow oil (C).
The obtained amine was brominated following Shulgin's method to yield 2.1 g 2C-B as the hydrochloride salt (D).

CONCLUSION:

It is possible to synthesize phenylethylamine derivatives different from PMA and PMMA using anethole as precursor. The total yield of 2,5-dimethoxybenzaldehyde from anethole varies between 15-25%. The total yield of 2C-B from 2,5-dimethoxybenzaldehyde amounts *ca.* 20% (using easily procurable compounds).

FIGURE 2a : The mass spectra of the intermediary products are shown: 2,5-dimethoxyphenyl-2-nitroethene [1], 2,5-dimethoxyphenyl-2-nitroethane [2], 2,5-dimethoxyphenylethylamine [3], 4-bromo-2,5-dimethoxyphenylethylamine (2C-B) [4]

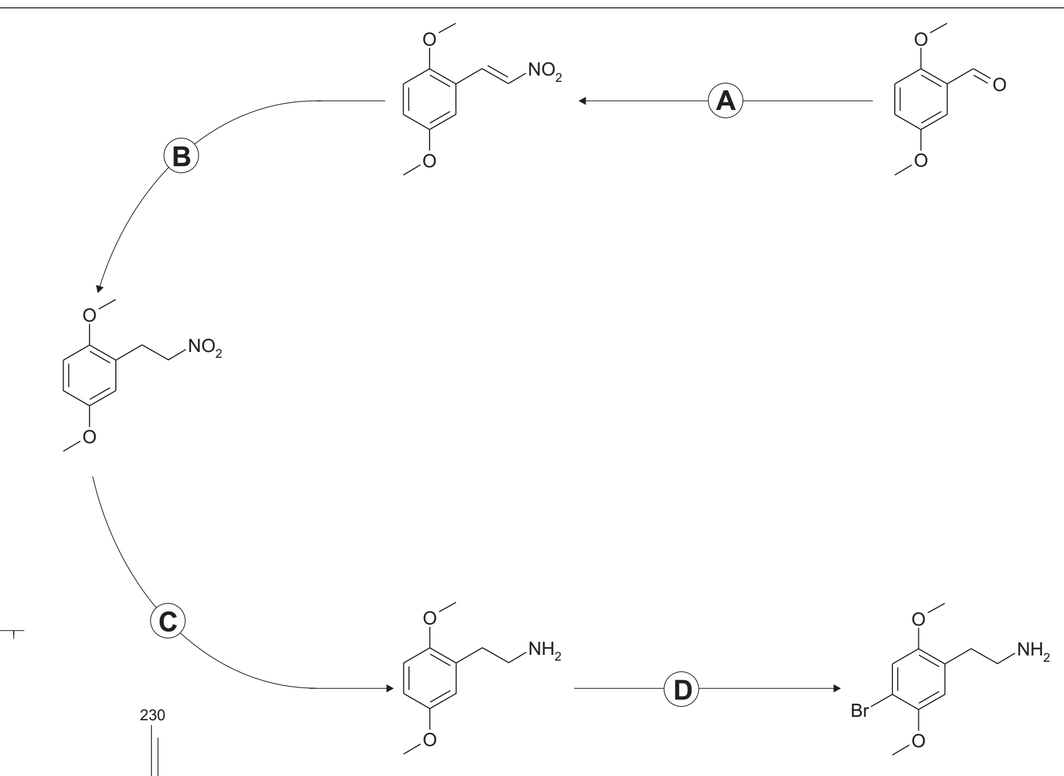

FIGURE 2b : 2,5-dimethoxybenzaldehyde is reacted with nitromethane to yield the corresponding nitrostyrene (A). The latter is reduced with sodium borohydride to the nitroethane (B). The nitro functional group is reduced by Zn/HOAc (C) and the obtained phenylethylamine is brominated to yield 2C-B (D).