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Assignment of batch membership of 3,4-methylenedioxy methylamphetamine hydrochloride by comparison of organic impurity profiles

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ABSTRACT

The illegal drug 3,4-methylenedioxymethylamphetamine, also known as MDMA, ecstasy or 'E', synthesised as the hydrochloride and then made into tablets, has organic impurities arising from manufacture that can be used to profile seized material. Knowing if two samples come from the same batch gives strategic information about the drug manufacturing trade. We report similarity measures (Pearson correlation coefficient, reported as the modified Pearson distance, and its Fisher transform) between impurity content of pairs of samples manufactured using four common reductive amination routes. Powder and tablets are compared using the *n*th root of GC–MS peak normalised areas of 8 or 31 impurities, (n = 2, 3, 4, 5, 10). Overall using 31 compounds with 4th root pre-treatment gave the best discrimination. PtO_2/H_2, and Al/Hg reductions were completely discriminated among batches while $NaBH_4$ and $NaBH_3CN$ routes gave around 4% false assignments. Synthesis parameters were systematically altered to determine what parameters have significant effects on the overall purity of the product and on the impurity profiles. The amount ratio of methylamine and MDP2P, and the temperature control of the reaction mixture were both significant. Comparison of modified Pearson's distances (r scaled to ∈[0–100]), the Fisher transform of r, and ROC curves are simple ways of providing initial evidence whether seized drugs originate from the same batch.

1. Introduction

The most widely used methods for organic impurity profiling of amphetamine type stimulants (ATS) are gas chromatography-mass spectrometry (GC–MS) and gas chromatography with flame ionisation detection (FID) [1–9]. Organic impurities (including by-products) are extracted into an organic solvent and then injected onto a GC column. The chromatogram shows the organic impurities present in the sample. This organic impurity profile can then be compared with other chromatograms to establish similarities and/or differences between samples and seizures. The peak areas of specific target compounds can be stored in a database and chemometric treatments can be applied to find similarities between samples. The application of chemometric methods to compare chromatograms is a fast screening method for highlighting potential links but ultimately a visual comparison of the chromatograms needs to be made, as well as incorporating analytical results from different analytical techniques[10]. However to be used routinely by police laboratories, methods must be easy to implement and intuitive in their use.

1.1. Synthesis of MDMA by reductive amination

In this paper we focus on four methods for synthesising 3,4-methylenedioxymethylamphetamine (MDMA) involving reductive amination of 3,4-methylenedioxyphenylpropan-2-one (MDP2P) using methylamine (Fig. 1). Typically, up to about 30 organic by-products are easily identified across different synthetic methods.

As synthesised, MDMA is an oil, which is crystallised as the hydrochloride salt before being made into tablets with tabletting agents such as cellulose and magnesium stearate. MDMA.HCl is sold as powder or in tablets, and the manufacture of tablets can be carried out in a different location, and after some time, from the synthesis of MDMA itself. The question addressed in this paper is: given seized MDMA.HCl, as a powder or tablet, can samples made from the same batch, or the same process, be distinguished from each other? We also consider the effect of changing reaction conditions in the synthesis of MDMA. In a similar study by Weyerman [9] an initial, untested, assumption was that the samples used in the study were: (i) from the same batch if they were from the same seizure and cannot be visually

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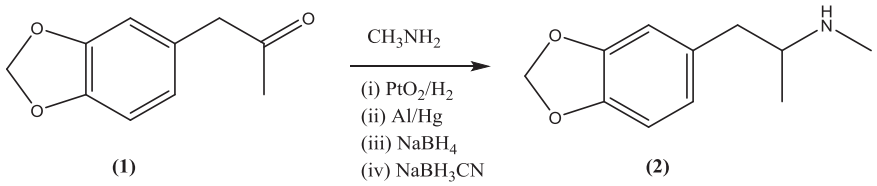

Fig. 1. The reductive amination of MDP2P (1) to MDMA (2).

differentiated; and (ii) from a different batch if they were from a different and unrelated seizure. The present paper aims to provide an objective assessment of the hypothesis.

2. Experimental

2.1. Materials

All reference standards and internal standards used in the chemical profiling were obtained from the reference collection of Australia's National Measurement Institute (NMIA). MDP2P was synthesised from methyl 3-[3',4'(methylenedioxy)phenyl]-2-glycidate[11]. Methylamine hydrochloride (98%), was obtained from Merck (Kilsyth, Vic, Australia). Other chemicals and solvents were obtained from chemical suppliers. For tabletting, magnesium stearate and microcrystalline cellulose were obtained from Bronson & Jacobs Pty Ltd (Homebush Bay, NSW, Australia). 'Egg' yellow dye and 'green lake' dye were purchased from Australian Food Ingredient Suppliers Pty Ltd (Brookvale, NSW, Australia).

2.2. Preparation methods

2.2.1. Preparation of MDMA from MDP2P by reductive amination using PtO_2/H_2, $NaBH_4$, and $NaBH_3CN$

MDMA was prepared from MDP2P and methylamine using PtO_2/H_2 described in Uncle Festers' 'Secrets of methamphetamine manufacture' with minor modifications [12]. MDMA was prepared from MDP2P with methylamine using $NaBH_4$ following the procedure outlined by Swist et al. [13]. MDMA was prepared from MDP2P with methylamine using $NaBH_3CN$ following the procedure outlined in our previous work [14,15].

2.2.2. Reductive amination of MDP2P with methylamine using Al/Hg Amalgam [16]

The preparation method is given here better to understand the changes made in the Plackett-Burman designed investigation described below (Section 2.3).

To Al foil (5 g, 2 mL) was added water (160 mL) containing mercuric chloride (0.12 g). The mixture was shaken and the amalgamation process allowed to proceed for 15 minutes. The water was then decanted and the foil washed with clean water and then decanted. To the foil was then added, in order, methylamine hydrochloride (7.6 g) in water (8 mL), isopropanol (23 mL), dilute sodium hydroxide solution (18 mL, 30% aq. soln.), MDP2P (6.7 g) and finally more isopropanol (45 mL). The reaction mixture was stirred and the temperature kept between 40–60 °C using an ice bath as required. The reaction was stirred for 3 hours and then filtered and rinsed with methanol. The methanol and isopropanol were removed using a rotary evaporator. To the reaction mixture was added water and then acidified with concentrated hydrochloric acid and unreacted MDP2P was extracted with dichloromethane. The remaining aqueous layer was basified with dilute sodium hydroxide solution and extracted with dichloromethane. The solvent was removed using a rotary evaporator leaving an orange oil (~4.5 g). The oil was dissolved in cooled isopropanol and acidified with concentrated hydrochloric acid. Diethyl ether was added resulting in precipitation of a crystalline material. The crystals were filtered, washed with a mixture of isopropanol and diethyl ether and dried yielding white crystals (~3.9 g), identified as MDMA hydrochloride by comparison of gas chromatographic retention time and mass spectrum with a certified reference standard of MDMA, and analysis by NMR and FTIR.

2.2.3. Preparation of MDMA tablets

MDMA hydrochloride powder was ground and homogenised using a mortar and pestle. The MDMA hydrochloride powder was subsampled and mixed with tabletting agent to give a purity of approximately 55–60%. The tabletting mix consisted of 95% microcrystalline cellulose, 5% magnesium stearate and 'egg yellow' dye. The mixture of MDMA hydrochloride and tabletting mix was then compressed into tablets using a tablet press machine. As a study of the effect of tabletting agents a batch of MDMA prepared by the $NaBH_4$ route was made up into tablets using the mixture detailed above, and one with 90% microcrystalline cellulose, 10% magnesium stearate and 'green lake' dye.

2.3. Changing synthesis conditions

An eight-experiment Plackett-Burman design ([17], Section 3.5) was used to investigate seven factors related to the conditions of synthesis that might affect the yield and impurity profile (see Table 4), with the Al/Hg route used to illustrate this approach. The Fisher z values were calculated (Eq. (3) below) from the correlation between impurity data in a synthesis under standard conditions and under the changed condition of the Plackett-Burman run. The synthesis under standard conditions was repeated four times and the standard deviation of z was calculated. The significance of effects was determined by a t-test between the effect and zero (H_0 is that there is no effect of the factor).

2.4. Chemical analysis

2.4.1. Purity of MDMA

The purity of MDMA hydrochloride powder was measured using an Agilent Technologies 7890A gas chromatograph with a flame ionisation detector (FID). A 0.32 mm i.d. ×30 m, 0.5 μm HP-5 column was used with helium carrier gas and N-phenylbenzylamine internal standard. The percentage of MDMA in the free base form was calculated using the GC/FID Agilent Technologies processing software to create a 5-point calibration curve from certified standards. Ten samples of powder from each batch were analysed for purity.

2.4.2. Organic Impurity profile

GC–MS analyses were performed using an Agilent Technologies 6890N gas chromatograph interfaced to an Agilent 5973N mass selective detector (MSD). A 0.20 mm i.d. × 25 m, 0.33 μm DB-1MS column was used with helium carrier gas at constant flow of 0.6 mL/min. The oven temperature was programmed from 90 °C (1 min) to 300 °C (10 min) at 8 °C/min. Injections (1 μL) were made in splitless mode (0.5 min) and a mass range of 35 to 500 amu was scanned. Ten samples of powder from each synthetic run, and ten samples from each batch of tablets (six in the case of Al/Hg) were analysed for impurities.

(i) *Sample preparation*

MDMA hydrochloride (100 mg) was dissolved in pH 7 phos-