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Characterization of Route Specific Impurities Found in Methamphetamine Synthesized by the Leuckart and Reductive Amination Methods

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Impurity profiling of seized methamphetamine can provide very useful information in criminal investigations and, specifically, on drug trafficking routes, sources of supply, and relationships between seizures. Particularly important is the identification of "route specific" impurities or those which indicate the synthetic method used for manufacture in illicit laboratories. Previous researchers have suggested impurities which are characteristic of the Leuckart and reductive amination (Al/Hg) methods of preparation. However, to date and importantly, these two synthetic methods have not been compared in a single study utilizing methamphetamine hydrochloride synthesized in-house and, therefore, of known synthetic origin. Using the same starting material, 1-phenyl-2-propanone (P2P), 40 batches of methamphetamine hydrochloride were synthesized by the Leuckart and reductive amination methods (20 batches per method). Both basic and acidic impurities were extracted separately and analyzed by GC/MS. From this controlled study, two route specific impurities for the Leuckart method and one route specific impurity for the reductive amination method are reported. The intra- and inter-batch variation of these route specific impurities was assessed. Also, the variation of the "target impurities" recently recommended for methamphetamine profiling is discussed in relation to their variation within and between production batches synthesized using the Leuckart and reductive amination routes.

Globally, methamphetamine is one of the most frequently abused drugs worldwide. It is mainly produced in North America (34%) and East and South-East Asia (62%). According to the 2008 World Drug Report,[3] methamphetamine production in Europe continues to be limited to only a few countries, notably the Czech Republic, the Republic of Moldova, and Slovakia. The National Association of Counties in America found that methamphetamine is the primary illegal drug in 47% of the states in the United States, a higher percentage than that of any other drug.[4]

Methamphetamine can be synthesized by one of several routes using either of two precursors. Each route results in an organic and inorganic impurity profile that is influenced by the precursors, reagents, and synthetic method used for production.[5] An important goal of impurity profiling is the identification of "route specific" impurities for each of the common methods, in this case, of methamphetamine manufacture. Route specific impurities are those which, when present in an illicit substance, indicate the use of a particular synthetic pathway. Impurity profiling therefore has the potential to be a useful tool for both evidential and intelligence purposes.

Synthesis methods for methamphetamine can be categorized according to the starting material used. Routes most commonly used in Asia and the U.S.A.,[6−8] such as the Nagai, Rosenmund, Birch, Emde, and Moscow methods, all require ephedrine or pseudoephedrine as a starting material. Two routes commonly used in Europe and the U.S.A., the Leuckart and reductive amination with aluminum/mercury (Al/Hg) amalgam techniques, both require 1-phenyl-2-propanone (P2P) as the starting material (see Figure 1). The route specific impurities for the two methods utilizing P2P within a single controlled study will be discussed in this paper.

Previous studies have focused on the identification of route specific impurities present in methamphetamine synthesized by the Nagai,[9] Emde,[10] and Leuckart[1] methods, and several analytical techniques have been utilized for the identification of both organic and inorganic impurities.[6,11] Previous work has been dominated by GC/MS analysis with one study investigating IRMS with gas

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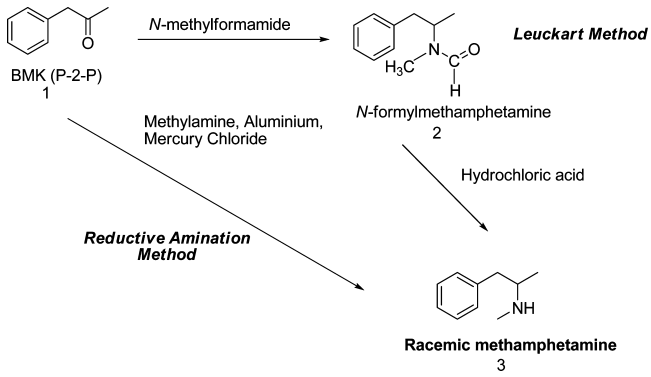

Figure 1. Methamphetamine synthesized from 1-phenyl-2-propanone (P2P).

chromatographic analysis for impurity profiling. Studies, however, are normally conducted on methamphetamine samples which have been seized by police authorities and of which the history is unknown; therefore, the unequivocal identification of route specific impurities is difficult. Furthermore, previous research[1,2] characterizing impurities present in methamphetamine synthesized by the Leuckart or reductive amination methods has *only* looked at one route or the other, rather than both pathways in conjunction with each other, by the same scientist and laboratory. The research presented here which involves in-house synthesized samples allows assessment of the variability of impurities *within* and *between* production batches where the provenance of the sample is definitively known.

Currently, the recommended methods for identifying links between methamphetamine samples relies on the relative concentrations of selected impurities present in samples. Thus, information on the variability of relative quantities of impurities from the same and different batches is crucial, as this will dictate the level at which links can be made (i.e., between samples from a single production batch or, more broadly, between samples from different production batches from the same chemist or laboratory).

In this study, 20 batches of methamphetamine were synthesized by the Leuckart method and 20 batches were synthesized by the reductive amination (Al/Hg) route. The preparative methods were taken from published materials which are accessible to and used by the clandestine chemist.[12] It should be noted that while every effort was used to exactly mimic the reaction conditions used for clandestine synthesis, safety considerations also influenced the synthesis and these may not be as stringently used in clandestine laboratories.

To obtain a broad spectrum of basic *and* acidic impurities in each batch, two impurity extracts (pH 6.0 and pH 10.5) were taken from the synthesized methamphetamine hydrochloride using an extraction method developed in-house from those published in the literature.[13,14] The acidic and basic extracts for each production batch were then analyzed by GC/MS using conditions based on those published by Inoue et al.[14] The combination of both acidic and basic impurity profiles has not previously been reported.

In this study, the intra- and inter-batch variation of 24 target impurities suggested by the CHAMP (Collaborative Harmonisation of Methods for Profiling of Amphetamine type Stimulants) method identified[5] in the in-house synthesized methamphetamine is discussed.

EXPERIMENTAL SECTION

Reagents and Materials. 1-Phenyl-2-propanone, *N*-methylformamide, and methylamine hydrochloride were purchased from Sigma-Aldrich, and all other chemicals and solvents were purchased from Fisher Scientific. Twenty batches of methamphetamine hydrochloride were synthesized by the Leuckart route, and 20 batches were synthesized by the reductive amination method, as outlined below.

Synthesis of Methamphetamine by the Leuckart Method.[12] To 1-phenyl-2-propanone (5.4 mL, 40.2 mmol) was added *N*-methylformamide (13.4 mL, 229 mmol, 5.7 equiv) with stirring. The temperature was gradually increased to 165−170 °C and held for 24−36 h. After cooling to room temperature, a 10 M NaOH solution (24 mL, 0.24 mmol) was added, and the reaction mixture refluxed for 2 h. After cooling to room temperature, the aqueous layer was discarded, and 37% HCl (10.7 mL, 0.004 mmol) added to the red organic layer. The mixture was refluxed for 2 h. After cooling to room temperature, an 8.3 M NaOH solution (16.0 mL, 0.13 mmol) was slowly added, and the crude methamphetamine base extracted with toluene (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, and the volatiles removed in vacuo to reveal the crude methamphetamine base as a brown oil. The crude methamphetamine base was distilled under vacuum (2 mbar, 60−100 °C) using Kugelrohr distillation to yield methamphetamine as a clear to pale yellow oil (2.5 g, 42%). Analysis was in agreement with published data for IR,[15] ^{1}H NMR and ^{13}C NMR.[16]

IR ν_{max} (film)/cm^{-1}: 1605 (N−C), 1454, 1373, 1155, 741, 697. ^{1}H NMR (400 MHz, $CDCl_3$): δH 1.08 (d, 3H, J = 8.0 Hz, CH_3), 2.42 (s, 3H, CH_3), 2.62 (dd, 1H, J = 20.0, 8.0 Hz, CH), 2.65 (dd, 1H, J = 20.0, 4.0 Hz, CH), 2.71−2.83 (m, 1H, CH), 7.17−7.37 ppm (m, 5H, C_6H_5). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.8, 34.0, 43.5, 56.4, 126.2, 128.4, 129.3, 139.5 ppm.

Conversion of the methamphetamine base to the hydrochloride salt was achieved by dissolving the base in toluene (50 mL) and bubbling through anhydrous hydrogen chloride gas until formation of a white precipitate. The resulting white precipitate was filtered, washed with toluene, and dried under high vacuum to produce methamphetamine hydrochloride as a white salt (2.0 g, 27%). Analysis was in agreement with published data for IR,[17] ^{1}H NMR,[1] and ^{13}C NMR.[18]

IR ν_{max} (KBr)/cm^{-1}: 3419 (N−H), 2971, 2731, 2461 (C−C), 1603 (N−C). ^{1}H NMR (400 MHz, D_2O): δH 1.22 (d, 3H, J = 8.0 Hz, CH_3), 2.64 (s, 3H, CH_3), 2.87 (dd, 1H, J = 24.0, 8.0 Hz,

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CH), 3.03 (dd, 1H, J = 20.0, 8.0 Hz, CH), 3.44−3.50 (m, 1H, CH), 7.25−7.38 (m, 5H, C_6H_5). ^{13}C NMR (100 MHz, D_2O): δ 14.8, 29.9, 38.8, 56.4, 127.5, 129.1, 129.5, 135.8 ppm.

Synthesis of Methamphetamine by the Reductive Amination Method.[12] To aluminum foil (2.9 g) cut into 2 cm squares was added distilled water (100 mL) containing mercuric chloride (0.067 g, 0.247 mmol). The amalgamation was allowed to proceed for 15 min. The water was then decanted, and the aluminum foil rinsed with distilled water (2 × 300 mL).

In a separate flask, NaOH (4.4 g, 109 mmol, 2.7 equiv) was dissolved in methanol (20 mL). Methylamine hydrochloride (7.2 g, 107 mmol, 2.7 equiv) was added, and the mixture cooled to −10 °C. 1-Phenyl-2-propanone (5.4 mL, 40.2 mmol) was then added to the solution.

The 1-phenyl-2-propanone solution was poured onto the activated aluminum with swirling. During this addition process, the flask was immersed in an ice bath as necessary to keep the temperature around 0 °C. After the addition process, the reaction mixture was heated to around 50−60 °C. After 90 min the reaction was complete (as determined by NMR of preliminary reaction runs). Celite was added to the alcohol solution containing the product. The resultant mixture was then filtered and rinsed with methanol. The combined organic layers were dried over $MgSO_4$ and the volatiles removed in vacuo to reveal the crude methamphetamine base as a pale yellow oil. The crude product was distilled according to the procedure detailed above to reveal a clear to pale yellow colored oil (4.09 g, 69%). The methamphetamine base was then converted to the hydrochloride salt, again, according to the procedure detailed above. Analyses were as described previously.

Extraction of Impurities from Methamphetamine Hydrochloride. *Basic Extract.* A 0.1 M phosphate buffer (pH 7.0) was brought to pH 10.5 by the addition of 10% Na_2CO_3. Synthesized methamphetamine hydrochloride (100 mg) was homogenized with a mortar and pestle and dissolved in the pH 10.5 phosphate buffer (2 mL). The mixture was sonicated (5 min) within a sonication bath, and vortexed (2 min) using a vortex mixer. Ethyl acetate (0.4 mL) containing eicosane (as an internal standard at 0.05 mg/mL concentration) was added. After centrifugation (5 min), the organic layer was transferred into a microvial insert for GC/MS analysis.

Acidic Extract. A 0.1 M acetate buffer (pH 8.16) was brought to pH 6.0 by addition of acetic acid. The pH 6.0 acetate buffer was used to extract acidic impurities from the synthesized methamphetamine in an identical fashion to that described above for the basic extraction.

GC/MS Analysis. GC/MS analysis was performed using an Agilent 6890 GC and a 5973 mass selective detector (MSD). The mass spectrometer was operated in the electron ionization mode at 70 eV. Separation was achieved with a non-polar capillary column (DB-1MS, 25 m × 0.2 mm i.d., 0.33 μm, J & W Scientific) with helium as the carrier gas at a constant flow rate of 1.0 mL/min. The oven temperature program adapted from Inoue et al.[14] started at 50 °C for 1 min, was increased to 300 °C at a rate of 10 °C/min, and then held at 300 °C for 15 min. A 1 μL aliquot of the impurity extract was injected in the splitless mode with a purge time of 1 min. The injector and the GC interface temperatures were maintained at 250 and 300 °C, respectively. Mass spectra were obtained in the full scan mode (30−550 amu).

RESULTS AND DISCUSSION

We wished to examine the potential for drug profiling to identify route specific impurities and the expected variation of these route specific variations due to the chemical synthetic process only. As a consequence the inter- and intra-batch variations reflected in the data are those derived from the synthesis only, with all other variables (chemist, reagents, glassware, analytical process, etc.) being held as constant as possible.

Impurities Common to Both the Leuckart and Reductive Amination Methods. To date, only one route specific impurity for Leuckart-synthesized methamphetamine has been suggested: *N*-formylmethamphetamine.[19,20] However, a study by Qi et al.[21] cast doubt on the "route specific" status of this impurity; the authors reported *N*-formylmethamphetamine in seized methamphetamine samples which were believed to have been synthesized from ephedrine (i.e., not from the Leuckart or reductive amination routes, which have P2P as the starting material). In the present work, *N*-formylmethamphetamine was found in *all* batches of methamphetamine, regardless of whether the Leuckart or reductive amination routes were used, thus confirming that *N*-formylmethamphetamine is not route specific for the Leuckart method of methamphetamine synthesis.

Previous work by Kram and Kreugal[1] identified several impurities present in methamphetamine hydrochloride known to have been synthesized by the Leuckart method: dibenzylketone, α-benzyl-*N*-methylphenethylamine, and *N*-methyldiphenethylamine. The authors recognized that, while these impurities were associated with the Leuckart synthesis, it was not possible to determine if they were route specific. Again all batches of methamphetamine synthesized in this study were found to contain all three of these impurities and, therefore, they cannot be deemed route specific for the Leuckart method.

Route Specific Impurities for the Leuckart Method. From comparison of the impurities present in methamphetamine synthesized by the Leuckart and reductive amination methods, it is possible to identify two impurities which are route specific for the Leuckart method. These are α,α′-dimethyldiphenethylamine and *N*,α,α′-trimethyldiphenethylamine. These two impurities were originally associated with the Leuckart method in the 1970's (by Barron et al.,[18] and Kram and Kreugal[1]), but it was not possible at that time to preclude them from being formed by other synthetic methods. In the present study, these two impurities were only identified in the samples synthesized by the Leuckart method. α,α′-Dimethyldiphenethylamine was detectable in both the basic and acidic extracts. Having stated this, the extraction of this specific impurity was more efficient under basic conditions (see Figure 2). Some of the impurities identified in the acidic and basic extracts of Leuckart-synthesized methamphetamine are displayed in Tables 1−2.

It is worthy of note that pyridines 7 and 14, which were identified in the CHAMP amphetamine and methamphetamine

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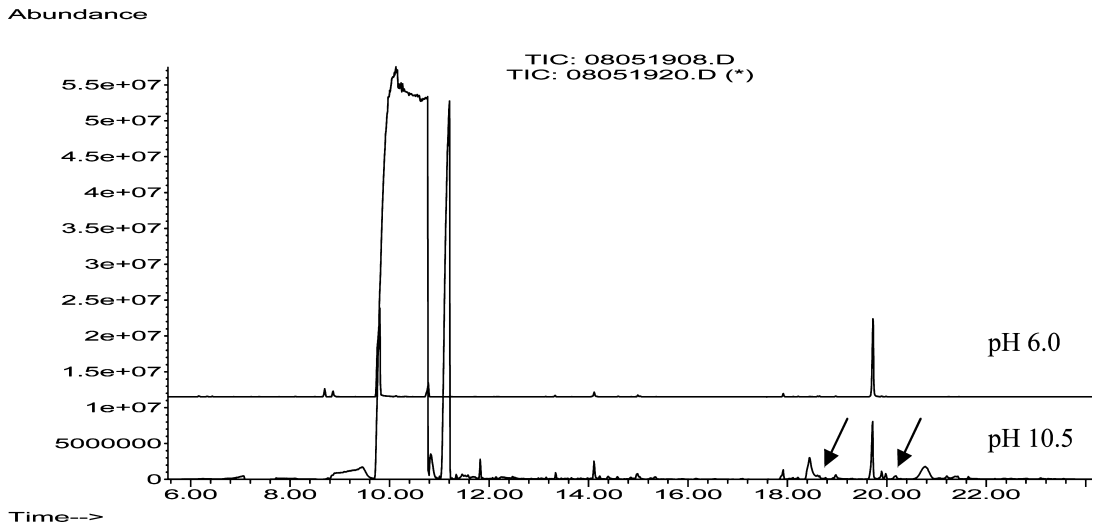

Figure 2. Impurity profile under basic and acidic conditions.

Table 1. List of Some of the Impurities Identified in the pH 6.0 Extract of Methamphetamine Synthesized by the Leuckart Route[a]

no.	RT	impurity extracted at pH 6.0	semiquantitative concentration mg/mL	intra-batch ($n = 6$) RSD	inter-batch ($n = 20$) RSD
1	8.705	1-Phenyl-2-propanone	5×10^{-3}	6%	37%
2	8.872	Amphetamine	5×10^{-3}	6%	39%
3	9.322	1-Phenyl-1,2-propanedione	2×10^{-4}	12%	80%
4	10.201	*N*-*N*-Dimethylbenzylamine	2×10^{-4}	34%	92%
5	10.786	Dimethylamphetamine (DMA)	1×10^{-2}	3%	121%
6	13.704	*N*-Formylamphetamine	2×10^{-4}	12%	72%
7	14.613	*N*-Formylmethamphetamine*	5×10^{-4}	16%	147%
8	15.052	*N*-Acetylmethamphetamine*	6×10^{-4}	12%	61%
9	18.461	Unidentified	7×10^{-4}	17%	69%
10	18.619	**α,α-Dimethyldiphenethylamine***	4×10^{-4}	**15%**	**59%**
11	18.661	**α,α-Dimethyldiphenethylamine***	5×10^{-4}	**15%**	**75%**
12	21.253	Pyridine 7 and 14*	2×10^{-5}	38%	73%
13	23.261	*N*-Methyl-*N*-(1-methyl-2-phenylethyl)-2-phenylacetamide*	5×10^{-3}	19%	63%

[a] RSDs were calculated using peak areas normalized to the sum of the CHAMP target impurities present in the relevant chromatogram. Route specific impurities for the Leuckart route are emboldened, and CHAMP target impurities are marked with an asterisk.

projects, are potentially route specific for the Leuckart route since they were found in all of the Leuckart batches only. However, these impurities can also be present in amphetamine samples; therefore, it is possible that detection of these impurities in methamphetamine samples could be the result of methamphetamine mixed with amphetamine, despite this combination being unlikely in our experience.

It is highly probable that the formation of *N*,α,α′-trimethyldiphenethylamine is as a result of the presence of methylamine within the reaction mixture. Two consecutive reductive amination processes, involving methylamine and the starting ketone, P2P, would ultimately lead to the production of *N*,α,α′-trimethyldiphenethylamine. To explain the origin of the aforementioned methylamine, careful consideration must be given to the proposed synthetic mechanism which leads to the production of methamphetamine via the Leuckart method. In this respect, during the initial iminium ion formation between P2P and *N*-methylformamide, hydroxide will be generated. Consequently, hydroxide-mediated hydrolysis of *N*-methylformamide leads to the production of residual methylamine (as well as the hydride required for the reduction of the intermediate iminium ion to deliver *N*-formylamphetamine). A second possible source of methylamine is as a contaminant in the commercially sourced *N*-methylformamide, as methylamine is a key component used within the industrial manufacture of *N*-methylformamide.

In relation to α,α′-dimethyldiphenethylamine, we propose that the formation of this species arises as a result of further specific impurities contained within the supplied *N*-methylformamide; these impurities are ammonia and formamide, and these species allow two possible routes into the second byproduct to be envisaged. First, ammonia could undergo two consecutive reductive amination processes with the starting ketone (vide supra), resulting in the direct formation of α,α′-dimethyldiphenethylamine. It is conceivable that ammonia may be present within the *N*-methylformamide as it is used in the large scale manufacture of methylamine, which, as discussed previously, is a key component in the production of *N*-methylformamide. In relation to the second impurity, formamide, it is plausible that *N*-formyl-α,α′-dimethyldiphenethylamine could be formed via two consecutive reductive amination processes involving formamide and the starting ketone. The subsequent acid-mediated hydrolysis (the second step of the Leuckart synthesis) would result in the production of the same α,α′-dimethyldiphenethylamine byproduct. Formamide is a likely impurity within the manufacture of *N*-methylformamide

Table 2. List of Some of the Impurities Identified in the pH 10.5 Extract of Methamphetamine Synthesized by the Leuckart Route[a]

no.	RT	impurity extracted at pH 10.5	semiquantitative concentration mg/mL	intra-batch ($n = 6$) RSD	inter-batch ($n = 20$) RSD
1	7.126	Acetic acid	1×10^{-2}	34%	74%
2	9.156	Amphetamine	3×10^{-2}	80%	67%
3	10.828	*N*-(1-Methyl-2-phenylethylidene)methenamine	3×10^{-3}	17%	104%
4	11.048	Dimethylamphetamine (DMA)	7×10^{-4}	30%	103%
5	13.672	*N*-Formylamphetamine	2×10^{-3}	28%	76%
6	14.331	Bibenzyl	1×10^{-3}	71%	114%
7	14.592	*N*-Formylmethamphetamine*	5×10^{-3}	62%	98%
8	15.031	*N*-Acetylmethamphetamine*	3×10^{-4}	42%	48%
9	16.286	Dibenzylketone*	3×10^{-4}	102%	115%
10	**17.917**	3,4-Diphenyl-3-buten-2-one*	2×10^{-4}	30%	237%
11	**18.043**	α-Benzyl-*N*-methylphenethylamine*	7×10^{-4}	39%	164%
12	18.116	Benzylmethamphetamine	7×10^{-5}	34%	229%
13	18.221	3,4-Diphenyl-3-buten-2-one*	9×10^{-3}	28%	180%
14	18.461	*N*-β-(Phenylisopropyl)benzyl methyl ketimine*	4×10^{-4}	22%	106%
15	**18.608**	**α,α-Dimethyldiphenethylamine***	$\mathbf{3 \times 10^{-4}}$	**30%**	**131%**
16	**18.649**	**α,α-Dimethyldiphenethylamine***	$\mathbf{2 \times 10^{-3}}$	**32%**	**136%**
17	18.858	*N*-Methyldiphenethylamine*	5×10^{-3}	33%	94%
18	**19.904**	**N-α,α-Trimethyldiphenethylamine***	$\mathbf{3 \times 10^{-3}}$	**28%**	**87%**
19	**19.988**	**N-α,α-Trimethyldiphenethylamine***	$\mathbf{2 \times 10^{-2}}$	**28%**	**82%**
20	**20.186**	*N*-Benzoylamphetamine	$\mathbf{9 \times 10^{-3}}$	**29%**	**66%**
21	20.406	*N*-Benzoylmethamphetamine	1×10^{-3}	35%	75%
22	21.065	2,6-Dimethyl-3,5-diphenylpyridine*	2×10^{-5}	48%	58%
23	21.211	Pyridine 7 and 14*	2×10^{-5}	32%	78%
24	22.34	*N,N*-Di-(β-phenylisopropyl)formamide	2×10^{-5}	30%	142%
25	23.25	*N*-Methyl-*N*-(1-methyl-2-phenylethyl)-2-phenylacetamide*	1×10^{-5}	40%	262%

[a] RSDs were calculated using peak areas normalized to the sum of the CHAMP target impurities present in the relevant chromatogram. Route specific impurities for the Leuckart route are emboldened, and CHAMP target impurities are marked with an asterisk (*).

due to residual ammonia present in the methylamine used in the production of this *N*-methylamide.

At this point it is worth considering how the quantities of these (route specific) impurities could be lessened. In relation to this, if the impurities were indeed being produced via the proposed pathways, we believe that their formation could be suppressed by careful manipulation of the reaction conditions employed. In this regard, if the route specific byproduct were the result of ammonia or methylamine contaminants within the sourced *N*-methylformamide, processes involving these volatile species could be suppressed by performing the reaction under (slightly) reduced reaction pressures. Alternatively, impurities arising from these same two amine species, as well as from formamide, within the commercially supplied *N*-methylformamide could be lessened by accessing a superior grade of this starting reagent. It should also be noted that *N*,α,α′-trimethyldiphenethylamine could form as a result of methylamine generated within the reaction manifold (vide supra). If this source of methylamine was, indeed, the route by which this trimethyl impurity was forming, this could be suppressed by increasing the equivalents of *N*-methylformamide with respect to the starting ketone. This amendment to the reaction protocol would increase the rate of formation of the desired and initially formed iminium ion, which would, in turn, reduce any undesired reductive amination processes and, ultimately, *N*,α,α′-trimethyldiphenethylamine byproduct formation.

Route Specific Impurities for the Reductive Amination (Al/Hg) Method. Comparison of the impurity profiles of methamphetamine synthesized by both methods reveals only one impurity which is route specific for reductive amination: 1-phenyl-2-propanol. This observation confirms that purported in 1989 in Verweij's review of the literature relating to impurities found in methamphetamine.[2] It is worth noting that this same impurity, 1-phenyl-2-propanol, was not detected in the basic impurity extract; the acidic extract was required for its detection (see Figure 3). Impurities identified in both extracts of reductive amination synthesized methamphetamine are given in Tables 3, 4.

With specific regard to 1-phenyl-2-propanol, it would appear that this impurity is formed by direct reduction of the starting ketone, P2P. Consequently, formation of this byproduct could be suppressed by prolonging the duration of the initial imine formation step of the overall process. This would serve to lower any quantities of unreacted starting ketone present in the reaction mixture at the stage when the subsequent reducing medium is introduced. In a further practical amendment, more complete removal of water from the generated amalgam would drive the ketone-to-imine equilibrium toward imine formation and, ultimately, lead to reduced levels of the alcohol byproduct, which results from reduction of the starting ketone.

Assessment of Intra- and Inter-batch Variation of Route Specific Impurities. The samples used in this study were synthesized by the same chemist using the same method, chemicals, and apparatus. Intra-batch variation, that is, variation of the quantities of impurities in separate extractions from one homogenized batch of methamphetamine, was assessed by performing impurity extractions of six sub-samples of a single batch of methamphetamine. Intra-batch variation is important because it affects how accurately samples from the same production batch can be linked together.

Inter-batch variation of selected impurities was also assessed. Inter-batch variation in this study is defined as the variation of the presence and quantities of impurities in extractions from different batches of methamphetamine synthesized by the same

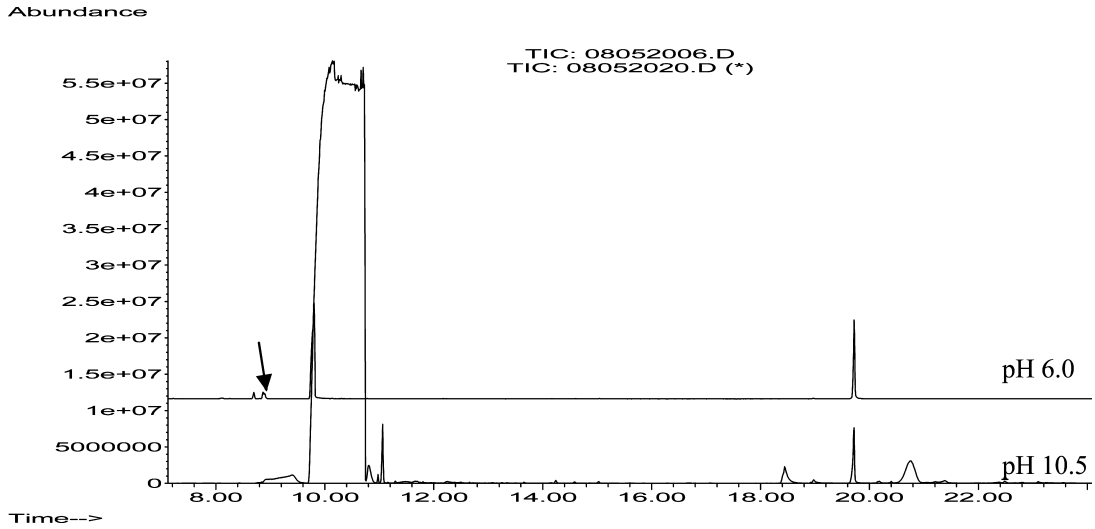

Figure 3. Impurity profile under basic and acidic condition.

Table 3. List of Some of the Impurities Identified in the pH 6.0 Extract of Methamphetamine Synthesized by the Reductive Amination Route[a]

no.	RT	impurity extracted at pH 6.0	semiquantitative concentration mg/mL	intra-batch (n = 6) RSD	inter-batch (n = 20) RSD
1	8.695	1-Phenyl-2-propanone	4×10^{-3}	3%	29%
2	8.873	Amphetamine	3×10^{-3}	7%	16%
3	**8.89**	**1-Phenyl-2-propanol**	$\mathbf{3 \times 10^{-3}}$	**6%**	**27%**
4	10.786	Dimethylamphetamine (DMA)	3×10^{-4}	6%	5%
5	14.603	*N*-Formylmethamphetamine*	2×10^{-4}	14%	16%
6	15.042	*N*-Acetylmethamphetamine*	4×10^{-4}	22%	20%

[a] RSDs were calculated using peak areas normalized to the sum of the CHAMP target impurities present in the relevant chromatogram. Route specific impurities for the reductive amination route are emboldened, and CHAMP target impurities are marked with an asterisk (*).

Table 4. List of Some of the Impurities Identified in the pH 10.5 Extract of Methamphetamine Synthesized by the Reductive Amination Route[a]

no.	RT	impurity extracted at pH 10.5	semiquantitative concentration mg/mL	intra-batch (n = 6) RSD	inter-batch (n = 20) RSD
1	7.034	Acetic acid	6×10^{-3}	55%	179%
2	9.408	Amphetamine	5×10^{-2}	49%	119%
3	10.715	*N*-(1-Methyl-2-phenylethylidene)methenamine	5×10^{-1}	15%	52%
4	11.06	Dimethylamphetamine (DMA)	3×10^{-2}	53%	98%
5	13.664	*N*-Formylamphetamine	3×10^{-3}	106%	109%
6	14.445	Bibenzyl	6×10^{-3}	144%	112%
7	14.584	*N*-Formylmethamphetamine*	2×10^{-2}	103%	77%
8	15.034	*N*-Acetylmethamphetamine*	2×10^{-2}	93%	142%
9	16.289	Dibenzylketone*	1×10^{-3}	100%	196%
10	17.92	3,4-Diphenyl-3-buten-2-one*	7×10^{-3}	166%	154%
11	18.014	α-Benzyl-*N*-methylphenethylamine*	8×10^{-4}	129%	164%
12	18.119	Benzylmethamphetamine	2×10^{-3}	138%	162%
13	18.192	3,4-Diphenyl-3-buten-2-one*	4×10^{-3}	131%	129%
14	18.453	*N*-β-(Phenylisopropyl)benzyl methyl ketimine*	6×10^{-2}	64%	77%
15	18.83	*N*-Methyldiphenethylamine*	2×10^{-3}	120%	153%
16	20.189	*N*-Benzoylamphetamine	4×10^{-3}	51%	82%
17	20.409	*N*-Benzoylmethamphetamine	1×10^{-2}	92%	118%
18	21.046	2,6-Dimethyl-3,5-diphenylpyridine*	3×10^{-2}	82%	173%
19	21.214	Pyridine 7 and 14*	2×10^{-2}	76%	65%
20	22.385	*N*,*N*-Di-(β-phenylisopropyl)formamide	5×10^{-3}	113%	89%
21	23.253	*N*-Methyl-*N*-(1-methyl-2-phenylethyl)-2-phenylacetamide*	4×10^{-3}	87%	108%

[a] RSDs were calculated using peak areas normalized to the sum of the CHAMP target impurities present in the relevant chromatogram. Route specific impurities for the reductive amination route are not present in the basic extract. CHAMP target impurities are marked with an asterisk (*).

chemist using the same preparative method. This translates to the ability of law enforcement to link together batches produced by the same clandestine laboratory or chemist.

The intra- and inter-batch variation were assessed in extraction using both pH 6.0 and pH 10.5 buffers, and for methamphetamine synthesized by both the Leuckart and reductive amination

methods. In each case the relative standard deviations (RSD) of the peak area of an identified impurity peak, normalized to the sum of the area of the "target impurities" suggested in the CHAMP profiling method,[5] was assessed.

Both isomers of the Leuckart route specific impurity α,α-dimethyldiphenethylamine had relatively high intra-batch variation indicated by RSDs of 30% and 32%. These RSDs increased significantly to 131% and 136%, respectively, when assessing inter-batch variation (see Table 2). Similar variability is observed for both isomers of the other Leuckart route specific impurity, *N*-α,α-trimethyldiphenethylamine: intra-batch RSDs for both isomers were 28%, which increased to 87% and 82% when calculating inter-batch RSDs (see Table 2).

Given the high intra-batch variability of the two Leuckart route specific impurities, it is not surprising that the inter-batch RSDs are also high. However, since the inter-batch RSDs are considerably greater than those from the intra-batch analyses, it is likely that variation in the quantities of the impurities occurs from batch to batch. This indicates that batches of methamphetamine produced by the same chemist using the same equipment, chemicals, and synthetic method would not be expected to contain consistent amounts of (at least) these key impurities from batch to batch.

The route specific impurity for the reductive amination route, 1-phenyl-2-propanol, has much lower variability. Intra-batch variation of this impurity (Table 3) is 6%, indicating that the quantity of this impurity is extracted and chromatographed consistently using six sub-samples from a single homogenized batch of methamphetamine. The inter-batch variation increases to 27%, indicating that there is some variation in the quantity of this impurity across 20 batches of methamphetamine synthesized by the same chemist using the same equipment, method, and reagents. Accordingly, the variability of the quantity of 1-phenyl-2-propanol in batches made by the same chemist may be too great to allow batch to batch linkage of the final products.

CONCLUSIONS

This is the first report where the impurities found in methamphetamine synthesized in-house from the same starting material (P2P) by both the Leuckart and reductive amination (Al/Hg amalgam) methods have been compared. Using both basic and acidic extracts with buffers at pH 10.5 and pH 6.0, respectively, it has been possible to identify two Leuckart route specific impurities present in the pH 10.5 extract: α,α-dimethyldiphenethylamine and *N*-α,α-trimethyldiphenethylamine (both isomers of each were present). Only one route specific impurity for the reductive amination method was identified, and this was found only in the acidic extract: 1-phenyl-2-propanol.

There are, of course, other methods used for methamphetamine manufacture, some of which are more common than those discussed here. The identification of route specific impurities for the Nagai, Rosenmund, Birch, Emde, and Moscow methods is currently underway in our laboratory and will be submitted for publication at a later date.

SUPPORTING INFORMATION AVAILABLE

The FT-IR and NMR spectra of the preparative compounds, the structures of impurities from both routes at each extracting pH, and the mass spectra of the route specific impurities for each route are presented together with additional chromatograms. This material is available free of charge via the Internet at http://pubs.acs.org.

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