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PAPER

CRIMINALISTICS

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Isolation and Identification of Three By-products Found in Methylamphetamine Synthesized by the Emde Route

ABSTRACT: This article describes the isolation and structural elucidation of three compounds produced during the synthesis of methylamphetamine by the so-called "Emde" procedure. The "Emde" procedure involves the preparation of the intermediate chloropseudoephedrine or chloroephedrine from ephedrine or pseudoephedrine, respectively. The intermediates are then reduced to methylamphetamine with hydrogen under pressure in the presence of a catalyst. The by-product compounds were isolated from methylamphetamine by column chromatography and liquid chromatography (LC). Proton nuclear magnetic resonance spectroscopy (^{1}H NMR), carbon nuclear magnetic resonance spectroscopy (^{13}C NMR), and nanospray quadrupole-time of flight-mass spectrometry (Q-TOF-MS) were used to identify them as two stereoisomers of the compound *N, N′*-dimethyl-3,4-diphenylhexane-2,5-diamine and *N*-methyl-1-{4-[2-(methylamino)propyl]phenyl}-1-phenylpropan-2-amine.

KEYWORDS: forensic science, chemical profiling, methylamphetamine, Emde reaction, *N, N′*-dimethyl-3,4-diphenylhexane-2,5-diamine, *N*-methyl-1-{4-[2-(methylamino)propyl]phenyl}-1-phenylpropan-2-amine

Methylamphetamine is a highly abused and addictive illicit drug (1). During 2000–2005, 49% percent of the world's amphetamine type stimulant (ATS) seizures were methylamphetamine (1). The drug is mainly produced in South-East Asia and North America (1) and can be manufactured via a number of synthetic pathways (Fig. 1) (2,3). A common clandestine synthesis is the reduction of (1*R*,2*S*)-(−)-ephedrine or (1*S*,2*S*)-(+)-pseudoephedrine, which yields *d*-methylamphetamine (4–7). Other methods include reduction of phenyl-2-propanone (P2P), which yields racemic or *dl*-methylamphetamine (8–11).

Regardless of which method is employed, all clandestinely produced methylamphetamine samples contain manufacturing by-products to varying degrees. The by-products are formed during the many side reactions that may take place between precursors, intermediates, impurities present in precursors, and the major synthetic products. Some by-products may also be formed because of poor storage conditions or the cutting agents that may be added. Certain manufacturing by-products may be specific to a synthetic route (9,12). Chemical profiling examines basic, acidic, and neutral by-products in methylamphetamine with the aim of identifying the synthetic route. This profiling can also provide information useful in establishing links between different drug seizures.

This article describes work performed to elucidate the structure of three manufacturing by-products produced during the "Emde" synthesis of methylamphetamine and to determine whether or not these three by-products are route-specific marker compounds for the "Emde" synthesis. The "Emde" synthesis involves the preparation of either chloropseudoephedrine or chloroephedrine from ephedrine or pseudoephedrine, respectively, followed by the reduction of the chloro intermediates to methylamphetamine with hydrogen gas under pressure and in the presence of a catalyst such as palladium on barium sulfate (13).

In 1929, Emde reported the detection of an unknown by-product in his methylamphetamine samples prepared by the same chloroephedrine to methylamphetamine method described in this article (13). Emde tentatively identifies this by-product as "didesoxyephedrine" (Fig. 2) (13). In 1951, Gero investigated the "Emde" reaction further and identified the by-product as *N, N′*-dimethyl-3,4-diphenylhexane-2,5-diamine, which is consistent with Emde's proposal (14). The structure proposed by Emde and Gero for this by-product is the same as identified in this article as *N, N′*-dimethyl-3,4-diphenylhexane-2,5-diamine.

Nanospray quadrupole-time of flight-mass spectrometry (Q-TOF-MS), ^{1}H NMR, ^{13}C NMR, and two-dimensional NMR experiments (including COSY, HMBC, HSQC, DEPT) were used to identify the three manufacturing by-products as two stereoisomers of the compound *N, N′*-dimethyl-3,4-diphenylhexane-2,5-diamine and *N*-methyl-1-{4-[2-(methylamino)propyl]phenyl}-1-phenylpropan-2-amine.

Materials and Methods

Reagents and Standards

All reference standards and internal standards used in the chemical profiling were obtained from the reference collection of the National Measurement Institute (Pymble, NSW, Australia).

(1*S*,2*S*)-(+)-Pseudoephedrine hydrochloride (99%), (1*R*,2*S*)-(−)-ephedrine hydrochloride (99%), tris(hydroxymethyl)aminomethane (99.9%), nonadecane (99%), ammonium bicarbonate, palladium 5 wt. % on barium sulfate reduced, platinum (IV) oxide, silica gel

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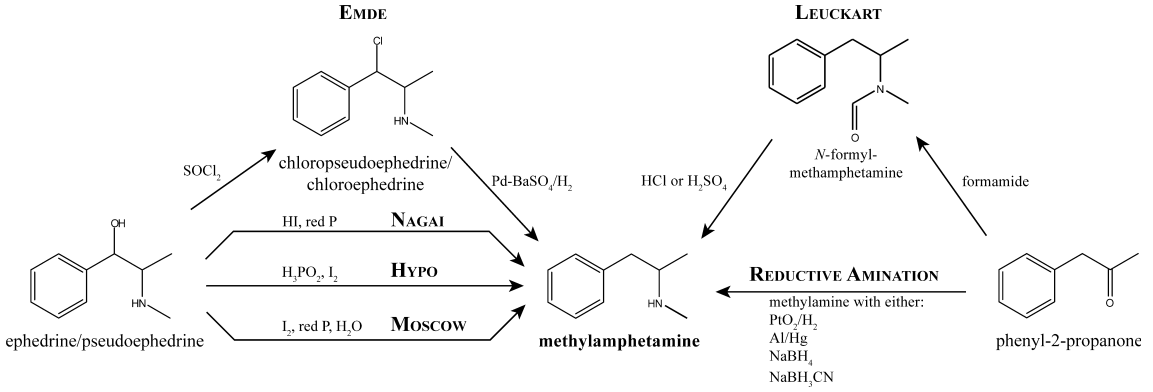


FIG. 1—*Synthesis routes for methylamphetamine.*

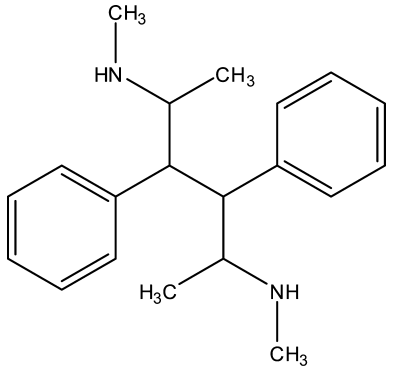


FIG. 2—*Structure of 'didesoxyephedrine' proposed by Emde (13).*

(200–400 mesh 60 Å), sodium borohydride (98%), and red phosphorus were obtained from Sigma–Aldrich (Castle Hill, NSW, Australia). Analytical grade isopropanol and diethyl ether, and GC grade hexane and toluene were obtained from Merck (Kilsyth, VIC, Australia). Analytical grade methanol and dichloromethane, and sodium acetate (anhydrous) were obtained from Mallinckrodt Chemicals (Philipsburg, NJ). Hydrochloric acid (36%), glacial acetic acid, sodium hydroxide pellets, sodium carbonate, mercuric chloride, iodine, hypophosphorus acid (50%), and acid-washed sand were obtained from UNIVAR Ajax Finechem (Seven Hills, NSW, Australia). Benzene and thionyl chloride were obtained from Riedel-deHaen (Seelze, Germany). Hydriodic acid (50%) was purchased from BDH Chemicals (Poole, England). Methylamine hydrochloride (98%), sodium cyanoborohydride, and phenyl-2-propanone (98%) were obtained from Fluka (Steinheim, Germany). All reagents were used without further purification.

Reactions

Synthesis of Chloroephedrine/Chloropseudoephedrine—A solution of chloroform and thionyl chloride was chilled in an ice-bath. To this was slowly added pseudoephedrine (or ephedrine) hydrochloride, and the mixture was stirred for several hours. Diethyl ether was then added resulting in precipitation of chloroephedrine (or chlorospeudoephedrine) hydrochloride. The product was washed with ether/chloroform and dried yielding chloroephedrine hydrochloride (13) (Fig. 1).

Synthesis of Methylamphetamine via "Emde" Route—Sodium acetate anhydrous and water were added to a flask and the mixture was made neutral with acetic acid. Palladium on barium sulfate and chloroephedrine hydrochloride were then added. The flask was attached to a Parr 3911 hydrogenation apparatus (Moline, Illinois). The air was removed from the flask by vacuum pump and flushed with hydrogen several times and then charged with hydrogen to 30 psi. The flask was mechanically shaken until uptake of hydrogen ceased. The catalyst was filtered off and washed with water. The combined reaction mixture and aqueous washings were basified with dilute sodium hydroxide solution and the methylamphetamine base was extracted with dichloromethane. The dichloromethane was removed using a rotary evaporator leaving methylamphetamine base as an oil. The oil was converted to the hydrochloride salt by dissolving it in cooled isopropanol and acidifying 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 methylamphetamine hydrochloride (13) (Fig. 1).

A total of nineteen 'Emde' preparations of (*2S*)-methylamphetamine were carried out. Fourteen were based on (*1S,2S*)-(+)-pseudoephedrine, three were based on (*1R,2S*)-(−)-ephedrine, and two were based on a mixture of (*1R,2S*)-(−)-ephedrine and (*1S,2S*)-(+)-pseudoephedrine.

Synthesis of Methylamphetamine via Reductive Amination of Phenyl-2-Propanone with Methylamine Using—Platinum oxide/hydrogen gas (PtO_2/H_2): In a flask was added methylamine hydrochloride, methanol, dilute sodium hydroxide solution, P2P, and platinum oxide. The flask was attached to a Parr 3911 hydrogenation apparatus (Moline, IL). The air was removed from the flask by vacuum pump and flushed with hydrogen several times and then charged with hydrogen to 45 psi. The flask was mechanically shaken until uptake of hydrogen ceased. The catalyst was filtered off and washed with methanol. To reaction mixture was added water and acidified with concentrated hydrochloric acid, and unreacted P2P was extracted with dichloromethane. Extraction of the methylamphetamine base and conversion to the hydrochloride salt was carried out as outlined earlier (Fig. 1).

Aluminum/mercury amalgam (Al/Hg): To Al foil was added water containing mercuric chloride. The mixture was shaken and the amalgamation process allowed to proceed for several minutes. The water was then decanted and the foil washed with clean water and then decanted. To the foil was then added methylamine hydrochloride in water, isopropanol, dilute sodium hydroxide solution, and P2P. The reaction mixture was stirred, and the temperature kept between 40 and 60°C using an ice-bath as required. The reaction was stirred for several hours and then filtered and rinsed with

methanol. The methanol and isopropanol were removed using a rotary evaporator. To reaction mixture was added water and acidified with concentrated hydrochloric acid and unreacted P2P was extracted with dichloromethane. The remaining aqueous layer was basified with dilute sodium hydroxide solution and extraction of the methylamphetamine base and conversion to the hydrochloride salt was carried out as outlined earlier.

Sodium borohydride ($NaBH_4$): To a solution of methylamine hydrochloride and methanol, kept at −5°C using an ice-bath with sodium chloride, was added dilute sodium hydroxide solution. To this was added P2P and $NaBH_4$. The reaction was stirred in the ice-bath for 24 h and then diluted with water. The reaction mixture was acidified with concentrated hydrochloric acid and unreacted P2P was extracted with dichloromethane. The remaining aqueous layer was basified with dilute sodium hydroxide solution and extraction of the methylamphetamine base and conversion to the hydrochloride salt was carried out as outlined earlier.

Sodium cyanoborohydride ($NaBH_3CN$): To a solution of methylamine hydrochloride and methanol was added P2P and $NaBH_3CN$. The mixture was stirred for 36 h at room temperature after which water containing concentrated hydrochloric acid was added. The unreacted P2P was extracted with dichloromethane and the aqueous layer was basified with dilute sodium hydroxide solution. Extraction of the methylamphetamine base and conversion to the hydrochloride salt was carried out as outlined earlier.

Synthesis of Methylamphetamine via ''Nagai'' Route—In a round bottom flask was added pseudoephedrine hydrochloride, red phosphorus, hydriodic acid, and boiling chips. The reaction was refluxed for 24 h after which it was allowed to come to room temperature. Extraction of the methylamphetamine base and conversion to the hydrochloride salt was carried out as outlined earlier (Fig. 1).

Synthesis of Methylamphetamine via ''Moscow'' Route—In a round bottom flask was added pseudoephedrine hydrochloride, red phosphorus, iodine, water, and boiling chips. The reaction was refluxed for 24 h after which it was allowed to come to room temperature. Extraction of the methylamphetamine base and conversion to the hydrochloride salt was carried out as outlined earlier (Fig. 1).

Synthesis of Methylamphetamine via ''Hypo'' Route—In a round bottom flask was added pseudoephedrine hydrochloride, iodine, hypophosphorous acid, and boiling chips. The reaction was refluxed for several hours after which it was allowed to come to room temperature. Extraction of the methylamphetamine base and conversion to the hydrochloride salt was carried out as outlined earlier (Fig. 1).

As a result of the sensitive nature of this topic, the exact synthetic details have been withheld.

Gas Chromatography/Mass Spectrometry (GC/MS)

The method used to profile the methylamphetamine samples was adopted from the European project: SMT-CT98-2277 – Development of a harmonized method for the profiling of amphetamine (15). 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. It was fitted with a 1 m × 0.25 mm i.d. deactivated, fused silica retention gap. Helium was used as the carrier gas in the constant flow mode at a flow rate of 0.6 mL/min. The injection port temperature was 280°C, and the MS interface temperature was 300°C. 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 50–500 m/z was scanned. A 990- μL, single-tapered, injection port liner with glass wool packing was employed for all injections.

Quadrupole-Time Of Flight-Mass Spectrometry (Q-TOF-MS)

Accurate mass to four decimal places was obtained using an Agilent 6510 nanospray-Q-TOF-MS (Agilent, J&W, Santa Clara, CA). An acetonitrile solution (0.1 μg/mL) of the samples was analyzed by direct infusion at 0.5 μL/min. The mass scan range was 100–500 m/z, and the capillary voltage was 1400 V. Five-minute scans were taken at an acquisition rate of 1 spectrum per second. Mass spectra were acquired and processed using MassHunter Workstation software (Agilent, J&W).

Nuclear Magnetic Resonance Spectroscopy (NMR)

All ^{1}H NMR and ^{13}C NMR spectra were acquired on a Bruker DMX600 spectrometer. Approximately 10 mg of sample was dissolved in 0.7 mL of deuterated chloroform and placed into a 5-mm NMR sample tube. For ^{1}H NMR, the field strength was 600.132 MHz, receiver gain was 32, and the number of scans taken was 16. The spectra were acquired at a temperature of 300 K with a sweep width of 10 ppm and a prescan delay of 5.5 μsec. For ^{13}C NMR spectra, the field strength was 150.920 MHz, the receiver gain 8192, and the number of scans taken was 2800. The spectra were acquired at a temperature of 300 K with a sweep width of 250 ppm and a prescan delay of 6.0 μsec.

Liquid Chromatography-Photodiode Array Detector (LC-PDA)–Fraction Collector

A Waters Acquity Ultra-High Performance Liquid Chromatograph (UPLC) consisting of Waters Acquity Sample Manager and Waters Acquity Binary Solvent Manager coupled to a Waters Acquity PDA detector (Waters, Milford, MA) was used to isolate by-product 1 and by-product 2. The system was attached to a Waters Fraction Collector III and operated using FRACTIONLYNX software (Waters, Milford, MA). The UPLC system was fitted with a Waters C18 X-Bridge column 4.6 mm × 150 mm, 3.5 μm. The column was operated at ambient temperature. The mobile phase was 10 mM aqueous ammonium bicarbonate and acetonitrile under isocratic conditions (70:30) at a flow rate 1.4 mL/min.

Sample Preparation for Methylamphetamine Profiling by GC–MS

The method used to prepare the methylamphetamine samples for profiling was adopted from the European project (SMT-CT98-2277) (15). Methylamphetamine hydrochloride (100 mg) was dissolved in tris(hydroxymethyl)aminomethane buffer (4 mL), vortexed for 10 sec, and placed on a Clements mixer for 1 h. The sample was centrifuged at 630×*g* for 8 min and filtered through 0.45 μm Teflon filter. Internal standard solution (250 μL) was added to the solution, which was then placed on the Clements mixer for 15 min. The solution was centrifuged at 630×*g* for 8 min and the upper toluene layer was removed and analyzed by GC/MS.

Preparation of Internal Standard Solution

Nonadecane internal standard solution (10 μg/mL) was prepared by dissolving nonadecane (25 mg) in toluene (100 mL), then diluted 10-fold in toluene.

Preparation of Ammonium Bicarbonate Buffer

A 10 mM solution of ammonium bicarbonate in water (pH 8.5) was prepared by mixing ammonium bicarbonate (790.6 mg) with water (1000 mL) in a volumetric flask. The solution was then filtered through 0.2-μm cellulose nitrate.

Isolation of By-product 1, By-product 2, and By-product 3 from Methylamphetamine Hydrochloride

Column Chromatography—Silica gel was dry packed to form a 20 cm × 4 cm column. The silica gel was washed with 500 mL of methanol/ethylacetate/ammonia (50:50:5) mobile phase. Acid-washed sand was added to the top of the column to a depth of 1 cm and the column again eluted with mobile phase (100 mL). Methylamphetamine hydrochloride (2.1 g), synthesized in "Reactions" was converted to the free base and dissolved in the mobile phase (1 mL). This solution was added to the top of the column and the column was eluted with the mobile phase (50 mL) then fractions (approximately 5–8 mL each) were collected. A total of 50 fractions were collected. GC/MS analysis of each fraction revealed fractions 12 and 13 contained by-product 1 and by-product 2 and fraction 20 through fraction 23 contained by-product 3 contaminated with some methylamphetamine. Fractions 12 and 13 were combined, and approximately 145 mg of the by-products and other minor impurities was recovered. Fractions 20–23 were combined and the purification repeated on a fresh column to afford 40 mg of by-product 3.

LC-PDA–Fraction Collector—The mixture of by-products 1 and 2 (also containing other minor impurities) was further purified using LC-PDA attached to a fraction collector. Injections (3 μL) of a 20 mg/mL acetonitrile solution of the mixture containing by-product 1 and by-product 2 were carried out. The run time was 7.5 min, and a total of 600 injections were conducted. Approximately 20 mg of by-product 1 and 15 mg of by-product 2 were isolated.

Results and Discussion

A total of 19 "Emde" preparations of (2*S*)-methylamphetamine were performed including 14 based on (1*S*,2*S*)-(+)-pseudoephedrine, three based on (1*R*,2*S*)-(−)-ephedrine, and two based on a mixture of (1*R*,2*S*)-(−)-ephedrine and (1*S*,2*S*)-(+)-pseudoephedrine. The methylamphetamine hydrochloride prepared from each of these reactions was profiled according to the European SMT project (15). Three main unidentified peaks were present in the GC/MS profiles from each of the 19 reactions at 19.2, 19.6, and 22.2 min (Fig. 3*A*). The by-products represented by these chromatographic peaks have been detected by other authors in methylamphetamine samples prepared by the "Emde" route but their structures have not been elucidated (16,17).

The mass spectra of the three by-products are shown in Fig. 3*B–D*, respectively, and match closely with the spectra reported by Ko et al. (16) and Lee et al. (17). Ko et al. (16) report the detection of an impurity, in methylamphetamine prepared by the "Emde" route, as characteristic of the "Emde" method. This impurity which the authors identify as "U-2" has a mass spectrum that closely matches by-product 3 (Fig. 3*D*) reported here in this article. Lee et al. (17) report five chromatographic peaks that they believe arise mainly from impurities formed during the synthesis of methylamphetamine via chloroephedrine. The mass spectra of two of these chromatographic peaks identified by Lee et al. as "5" and "7" closely match spectra reported here for by-product 1 (Fig. 3*B*) and by-product 3 (Fig. 3*D*), respectively. Peak "7" was also reported to be detected in two of the five methylamphetamine samples prepared by the "Moscow" route (Fig. 1).

Isolation and Identification of By-product 1

The mass spectrum of by-product 1 gave m/z fragments of 58(100), 239(20), 118(17), 193(10), 147(7), and 208(5) (Fig. 3*B*). The results of the Q-TOF-MS gave the relative isotopic mass of the molecule as 296.2255 (calculated 296.2252) and confirmed the molecular formula to be $C_{20}H_{28}N_2$. The structure of the isolated by-product was elucidated by 1D and 2D NMR (see Table 1) and identified as *N, N′*-dimethyl-3,4-diphenylhexane-2,5-diamine (Fig. 4).

The ^{1}H NMR spectral assignments are given in Table 1. The symmetry of the ^{1}H NMR spectrum (Fig. 5) suggests that by-product 1 is a symmetrical dimer. The results also indicate that the two benzylic carbons are most likely attached to each other. The multiplet at 3.25 ppm represents the two benzylic protons H3 and H4, which are coupled to the protons at H2 and H5. Additionally, while the two benzylic protons are chemically equivalent, they are magnetically nonequivalent; thus, the spin system is second order.

The ^{13}C NMR spectral assignments are given in Table 1 and confirm the presence of four distinct aliphatic carbons and four distinct aromatic carbons. This confirms that the dimer is symmetrical as each corresponding carbon in each of the methylamphetamine moieties has equivalent chemical shifts. DEPT experiments confirmed the absence of methylene groups. This is consistent with the structure shown in Fig. 4.

The HMBC results shown in Table 1 reveal that the proton at position 3 (δ 3.25 ppm) shows a strong correlation with the aliphatic carbons at positions 1 (18.21), 2 (54.87), 4 (52.39), 5 (54.87), and with the aromatic carbons at positions Ar-1' (139.37), Ar-2' (130.22), Ar-6' (130.22), thus confirming the structure suggested in Fig. 4. Similarly, the proton at position 4 (δ 3.25 ppm) shows a strong correlation with the benzylic carbon at position 3 (52.39) and with the aromatic carbons at the *ipso* (139.37) and *ortho* (130.22) positions, therefore confirming the bond between the two benzylic carbons.

Isolation and Identification of By-product 2

The mass spectrum of by-product 2 gave m/z fragments of 58(100), 239(9), 193(2) (Fig. 3*C*). The results of the Q-TOF-MS gave the relative isotopic mass of the molecule as 296.2249 (expected 296.2252) and confirmed the molecular formula to be $C_{20}H_{28}N_2$. The structure of the isolated by-product was elucidated by 1D and 2D NMR (Table 2) and identified as another diastereomer of *N, N′*-dimethyl-3,4-diphenylhexane-2,5-diamine (Fig. 6).

The ^{1}H NMR spectrum (Fig. 7) confirmed the presence of 16 aliphatic protons and ten aromatic protons. The ^{1}H NMR spectral assignments are given in Table 2. The ^{13}C NMR spectral assignments are given in Table 2 and confirm the presence of eight distinct aliphatic carbons. The doubling up of peaks in the ^{1}H and ^{13}C NMR suggests that the dimer is nonsymmetrical.

DEPT experiments confirmed the absence of methylene groups. This is consistent with the structure shown in Fig. 6. COSY experiments (Fig. 8) demonstrate the connectivity of the molecule as shown in Fig. 6. The methyl protons at 0.73 ppm show coupling with the methine proton at 2.39 ppm. This methine proton at

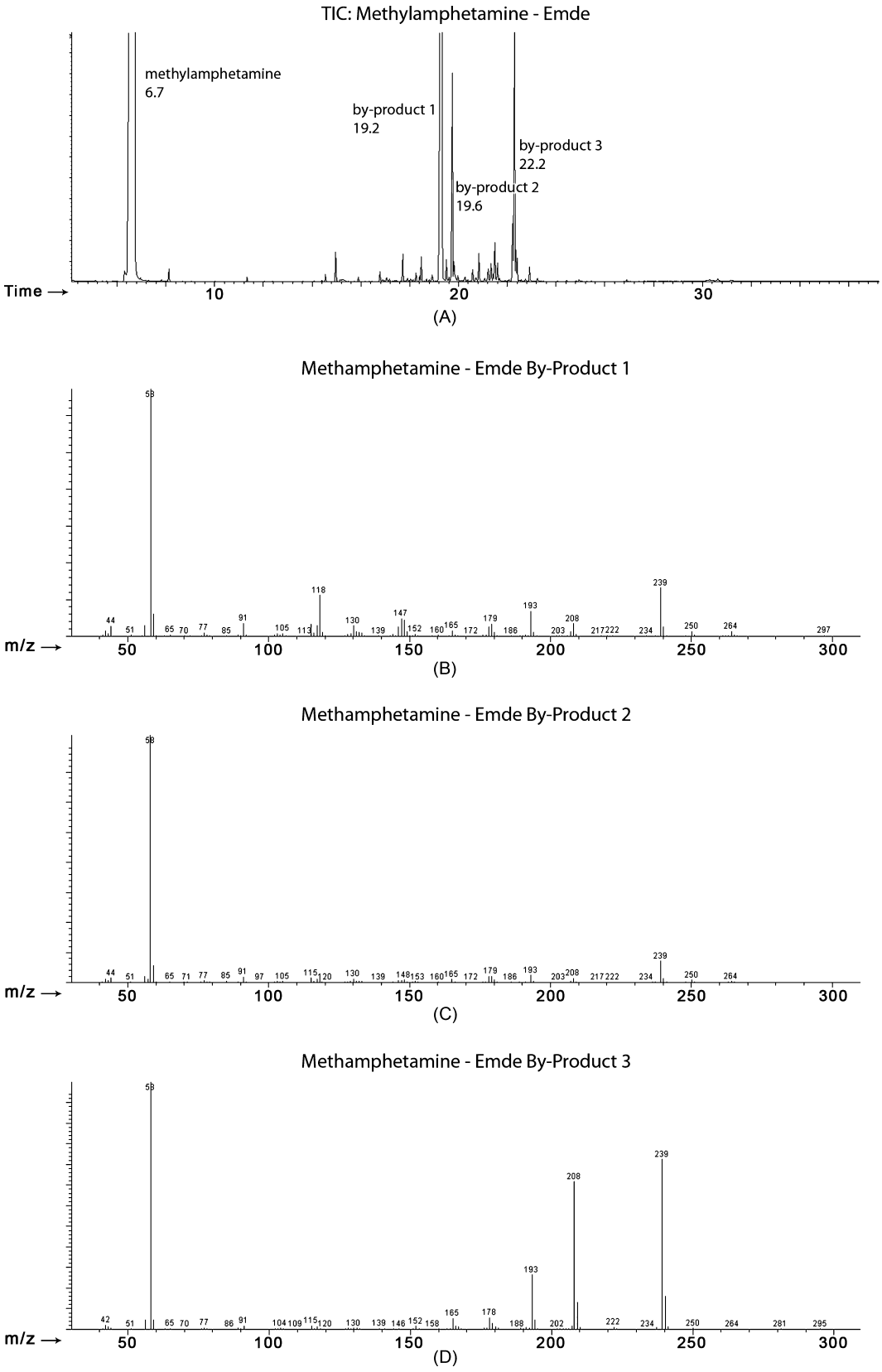
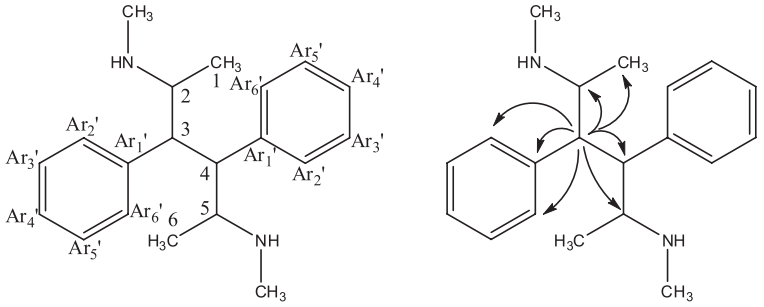


FIG. 3—*(A) GC trace of "Emde" methylamphetamine, (B) mass spectrum of by-product 1, (C) mass spectrum of by-product 2, and (D) mass spectrum of by-product 3.*

2.39 ppm shows coupling with the benzylic proton at 2.97 ppm. This benzylic proton also shows coupling to the other benzylic proton at 3.85 ppm which in turn shows coupling to the methine proton at 2.46 ppm. The proton at 2.46 ppm is also coupled to the methyl protons at 0.84 ppm. These results support the structure of the molecule as shown in Fig. 6.

TABLE 1—*^{1}H NMR, ^{13}C NMR, and HMBC data obtained for by-product 1.*



Assignment	Proton Shift (ppm) No. of Protons	Carbon Shift (ppm)	HMBC (ppm)
C1,6	1.19, 6H, doublet $J_{1,2}$ = 6.1 Hz, $J_{6,5}$ = 6.1 Hz	18.21	52.39, 54.87
N-CH_3	2.29, 6H, singlet	34.11	54.87
C2,5	2.84, 2H, multiplet	54.87	18.21, 34.11, 52.39, 130.22
C3,4	3.25, 2H, multiplet	52.39	18.21, 54.87, 130.22, 139.37
Ar-$C_{2',6'}$	6.84, 4H, doublet $J_{2',3'}$ = 5.5 Hz, $J_{6',5'}$ = 5.5 Hz	130.22	52.39, 126.21, 127.48
Ar-$C_{4'}$	7.09, 2H, multiplet	126.21	127.48, 130.22
Ar-$C_{3',5'}$	7.10, 4H, multiplet	127.48	130.22, 139.37
Ar-$C_{1'}$	–	139.37	–

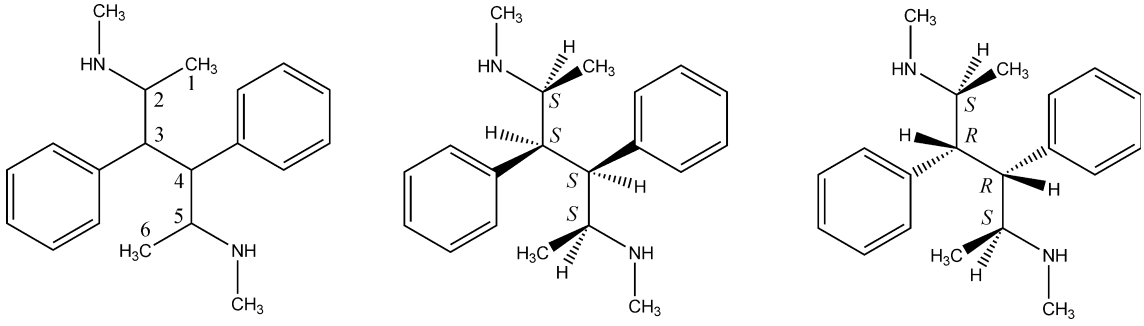


FIG. 4—*Structure of by-product 1.*

The HMBC results (Table 2) show that the proton at position 3 (δ 2.97 ppm) shows a strong correlation with the aliphatic carbons at positions 1 (18.74 ppm), 2 (55.17 ppm), 4 (49.01 ppm), 5 (55.13 ppm), and with the aromatic carbon at 139.76 ppm, thus confirming the structure suggested in Fig. 6. Similarly, the proton at position 4 (δ 3.85 ppm) shows a strong correlation with the benzylic carbon at positions 3 (53.55 ppm) and the aliphatic carbons at position 2, 5, and 6 and with the aromatic carbon at 139.76 ppm, therefore confirming the bond between the two benzylic carbons.

The doubling up of all aliphatic peaks in the ^{1}H NMR spectrum for by-product 2, suggests that all the methine protons are in different chemical environments. This can be explained by considering the stereochemistry of the molecule (Figs. 4 and 6). Ephedrine and pseudoephedrine have *S* configuration at the carbon attached to the methyl amino group. Previous studies conducted on the "Emde" reaction have shown that the configuration of the starting material at this position is retained in the final product (4). As a result, we would expect that in our dimer molecule, these two carbons (C2 and C5) would retain the *S* configuration of the starting material. This leaves two chiral centers (C3 and C4) that need to be considered when determining the structures of by-products 1 and 2. There are only three possible structures as shown in Figs. 4 and 6.

The ^{1}H NMR spectrum for by-product 1 indicates that the methine protons at C3 and C4 are chemically equivalent as are the methine protons at C2 and C5. The structures shown in Fig. 4 are the only two possibilities that fulfill these criteria, therefore by-product 1 has *2S,3S,4S,5S* or *2S,3R,4R,5S* configuration. As for by-product 2, the ^{1}H NMR spectrum indicates that the methine protons at C3 and C4 are distinct as are the methine protons at C2 and C5 which supports the structure having an *2S,3R,4S,5S* configuration as shown in Fig. 6.

Isolation and Identification of By-product 3

The mass spectrum of by-product 3 gave m/z fragments of 58(100), 239(68), 208(60), 193(22), 178(4), 165(4) (Fig. 3*D*). The results of the Q-TOF-MS gave the relative isotopic mass of the molecule as 296.2254 (expected 296.2252) and confirmed the molecular formula to be $C_{20}H_{28}N_2$. The structure of the isolated by-product was elucidated by 1D and 2D NMR (see Table 3) and identified as *N*-methyl-1-{4-[2-(methylamino)propyl]phenyl}-1-phenylpropan-2-amine (Fig. 9).

The ^{1}H NMR spectrum (Fig. 10) supports the presence of 17 aliphatic protons and nine aromatic protons. These results suggest that

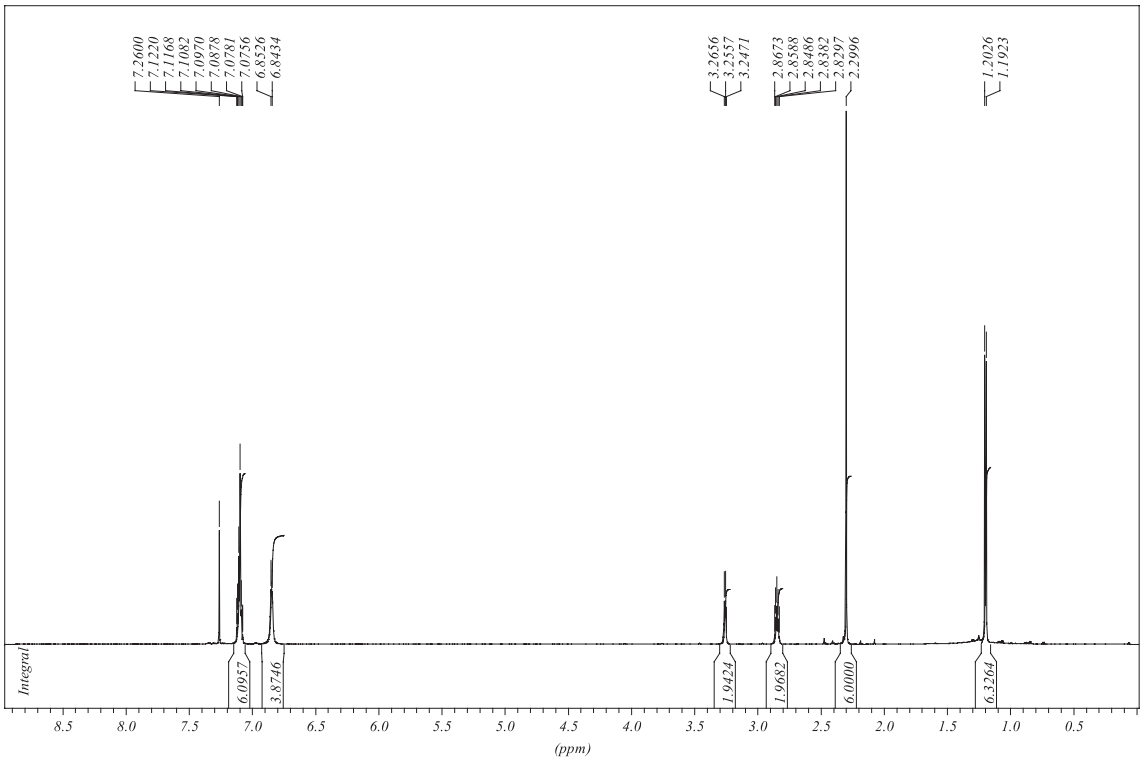
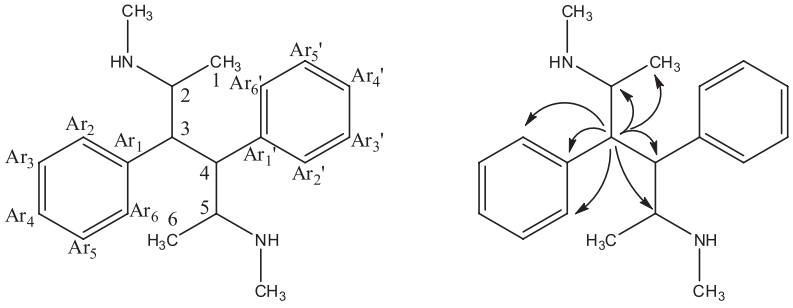


FIG. 5—*^{1}H NMR of by-product 1.*

TABLE 2—*^{1}H NMR, ^{13}C NMR, and HMBC data obtained for by-product 2.*



Assignment	Proton Shift (ppm) No. of Protons	Carbon Shift (ppm)	HMBC (ppm)
C1	0.73, 3H, doublet, $J_{1,2}$ = 6.4 Hz	18.74	53.55, 55.17
C6	0.84, 3H, doublet, $J_{6,5}$ = 6.6 Hz	14.98	49.01, 55.13
N-CH_3	2.06, 3H, singlet	34.69	–
N′-CH_3	2.32, 3H, singlet	33.61	–
C2	2.39, 1H, multiplet $J_{2,1}$ = 6.4 Hz, $J_{2,3}$ = 2.9 Hz	55.17	18.74, 49.01, 53.55, 139.76
C5	2.46, 1H, multiplet $J_{5,6}$ = 6.6 Hz, $J_{5,4}$ = 3.7 Hz	55.13	14.98, 49.01, 53.55, 139.76
C3	2.97, 1H, doublet of doublets $J_{3,4}$ = 12.1 Hz, $J_{3,2}$ = 2.9 Hz	53.55	18.74, 49.01, 55.13, 55.17, 139.76
C4	3.85, 1H, doublet of doublets $J_{4,3}$ = 12.1Hz, $J_{4,5}$ = 3.6 Hz	49.01	14.98, 53.55, 55.13, 55.17, 139.76
Ar-$C_{4'}$ Ar-C_4	7.26, 2H, multiplet	126.44, 126.47	128.02, 128.06, 129.95
Ar-$C_{2',6'}$ Ar-$C_{2,6}$	7.31, 4H, doublet	129.95 (broad)	126.44, 126.74, 128.02, 128.06
Ar-$C_{3',5'}$ Ar-$C_{3,5}$	7.35, 4H, multiplet	128.02, 128.06	126.44, 126.74, 129.95
Ar-$C_{1'}$ Ar-C_1	–	139.76	–

by-product 3 is a nonsymmetrical dimer with a di-substitution on one of the two aromatic rings. The chemical equivalence of the two sets of aromatic protons Ar-2′, Ar-6′ (7.20 ppm) and Ar-3′, Ar-5′ (7.06 ppm) suggests that the two benzylic groups substituted on the one aromatic ring are *para* to each other. The ^{1}H NMR spectral assignments are given in Table 3.

The ^{13}C NMR spectral assignments are given in Table 3 and confirm the presence of eight aliphatic carbons and eight distinct

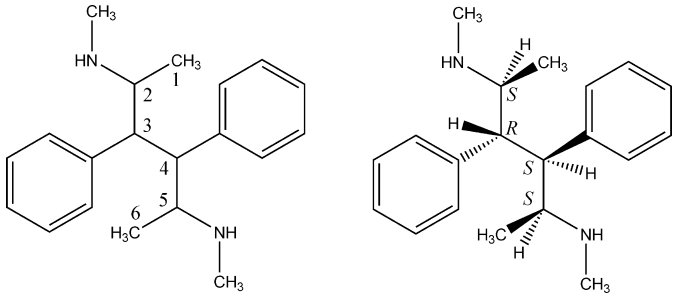


FIG. 6—*Structure of by-product 2.*

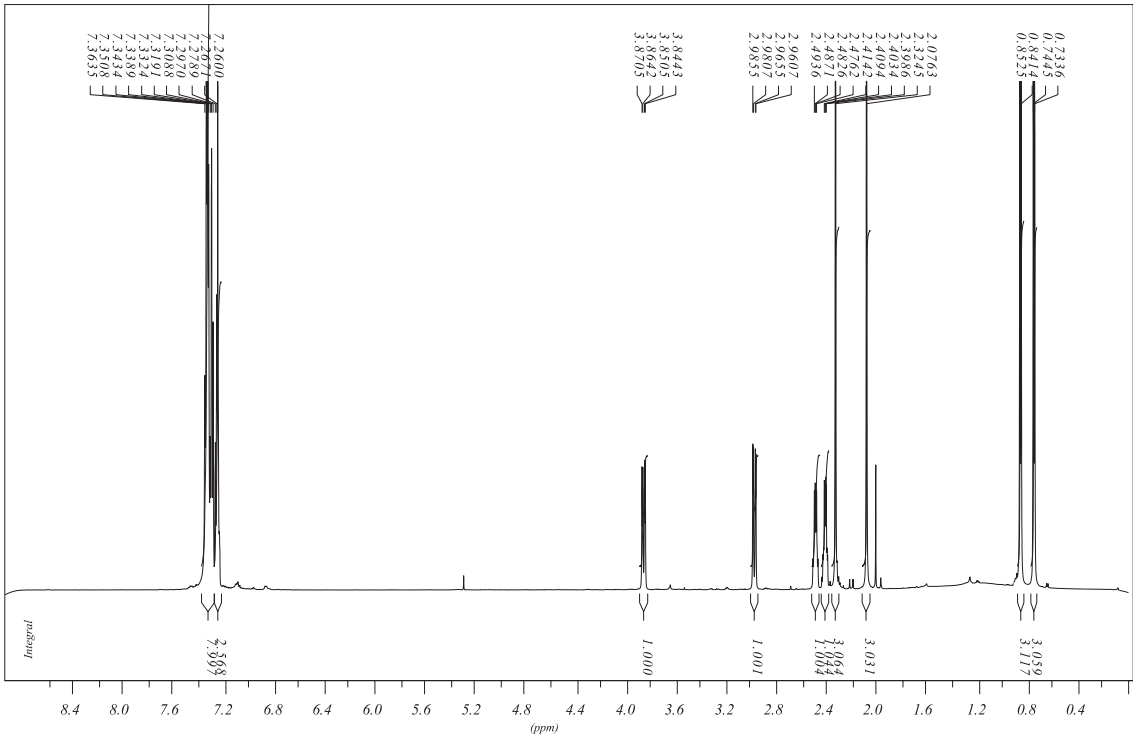


FIG. 7—*^{1}H NMR of by-product 2.*

aromatic carbons. DEPT experiments show the presence of one methine group, which is consistent with the structure shown in Fig. 9. The DEPT experiments also show the presence of three aromatic carbons with no protons attached to them, confirming the di-substitution of one of the aromatic rings and mono-substitution of the other aromatic ring.

The HMBC experiments (Table 3 and Fig. 11) revealed a strong correlation of the proton at position 1 (δ 3.70 ppm) and the aromatic carbons at Ar-1 (142.70), Ar-1′ (141.02), Ar-2 and Ar-6 (128.07), Ar-2′ and Ar-6′ (128.14), and the aliphatic carbons at 2 (57.83) and 3 (17.79), thus confirming this benzylic carbon is attached to two aromatic rings. Furthermore, these results confirm the *para*-substitution of the two benzylic groups. The diastereotopic methylene protons at position 1′ (δ 2.54 ppm and δ 2.63 ppm) show strong correlation to the aromatic carbons at position Ar-4′ (137.30), Ar-3′, and Ar-5′ (129.39) and the aliphatic carbons at 2′ (56.16) and 3′ (19.61). Table 3 details the strong correlation between the proton at position 2 (δ 3.31 ppm) and the aliphatic carbons at position 1 (58.92), 3 (17.79), and the *N*-methyl group (33.93), and the aromatic carbons at Ar-1 (142.70) and Ar-1′ (141.02). These results are all in agreement with the proposed structure (Fig. 9).

The three by-products were synthesized in greater yield using the same method as described by "Emde" (13) but substituting palladium on barium sulfate for platinum oxide. The catalyst affected the reaction by increasing the yield of each of the three by-products by up to 300-fold. By-products 1, 2, and 3 were isolated as outlined earlier in the Materials and Methods section and analyses by GC/MS and NMR identified the compounds as (2*S*,3*S*,4*S*,5*S*) or (2*S*,3*R*,4*R*,5*S*)—*N, N*′-dimethyl-3,4-diphenylhexane-2,5-diamine (Fig. 4), (2*S*,3*R*,4*S*,5*S*)—*N, N*′-dimethyl-3,4-diphenylhexane-2,5-diamine (Fig. 6) and *N*-methyl-1-{4-[2-(methylamino)propyl]phenyl}-1-phenylpropan-2-amine (Fig. 9), respectively.

The "Emde" reaction was monitored by GC/MS at various time intervals (1, 3, 7, 15, 25, 35, 55, 85 min). After 1 min, methylamphetamine had started to form including by-product 1 and 2. After 3 min, methylamphetamine had increased in yield and so too had by-products 1 and 2 and at this point by-product 3 was also detected. At 25 min, the reaction appeared to have come to completion as no more hydrogen was being absorbed. The reaction was

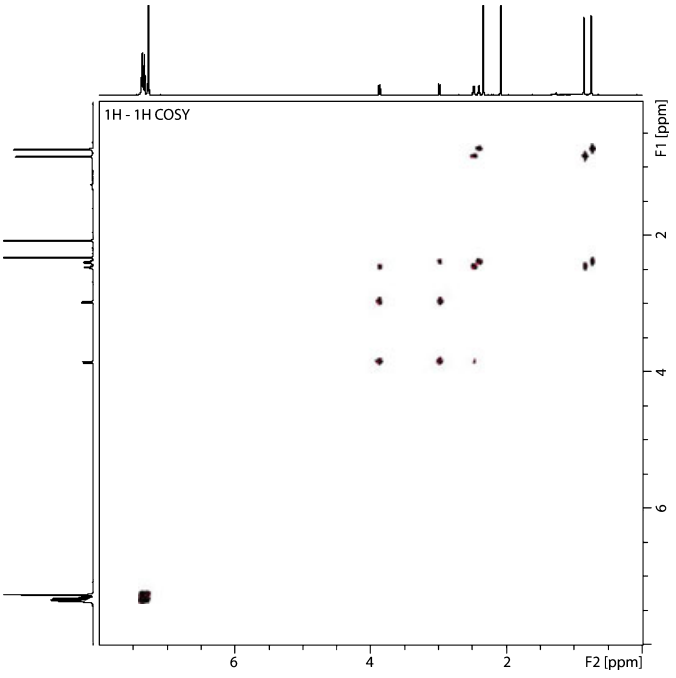


FIG. 8—*COSY NMR of by-product 2.*

continued under pressure and analyzed by GC/MS at 35, 55, and 85 min. At each of these time intervals, there appeared to be no significant variation in the relative peak area ratio of the by-products to the methylamphetamine.

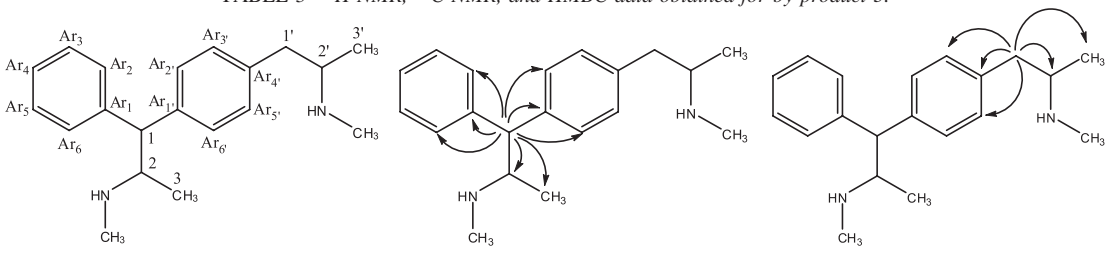
The reaction was also conducted without the addition of acetic acid and no change in methylamphetamine and by-product yields was observed. When the reaction was conducted under dilute conditions, i.e., a 10-fold dilution, it was observed that by-product formation had decreased significantly.

Multiple syntheses of methylamphetamine hydrochloride (29 in total) were also carried out using other common synthetic routes. Sixteen methylamphetamine samples were prepared via reductive amination reactions of P2P with methylamine using the catalysts/hydrogen source: (i) PtO_2 (four reactions); (ii) Al/Hg amalgam (four reactions); (iii) $NaBH_4$ (four reactions); and (iv) $NaBH_3CN$ (four reactions). Five methylamphetamine samples were synthesized by reduction of pseudoephedrine with hydriodic acid and red phosphorus ("Nagai" method). Four methylamphetamine samples were produced by reduction of pseudoephedrine with iodine and red phosphorus in water ("Moscow" method) and four methylamphetamine samples were prepared by reduction of pseudoephedrine with hypophosphorous acid and iodine ("Hypo" method).

The methylamphetamine hydrochloride prepared from each of these reactions was profiled using GC/MS and the organic impurity profiles were analyzed. The following results were observed: (i) by-product 1 and 2 were detected in methylamphetamine prepared by the "Emde" route but not by any other synthetic route; (ii) by-product 3 was only detected at concentrations with a signal to noise ratio greater than 3:1, in methylamphetamine prepared by the "Emde" route. In two of the four "Moscow" methylamphetamine samples, by-product 3 was detected but with a signal to noise less than 2:1; and in one of the four "Nagai" methylamphetamine samples, by-product 3 was detected at the noise level.

Earlier, it was noted that both Emde and Gero identified a by-product in methylamphetamine prepared by the same chloroephedrine to methylamphetamine method described in this article. The authors tentatively identified this by-product as "didesoxyephedrine" (Fig. 2), which has been identified in this article as *N, N′*-dimethyl-3,4-diphenylhexane-2,5-diamine. Gero describes a

TABLE 3—*^{1}H NMR, ^{13}C NMR, and HMBC data obtained for by-product 3.*



Assignment	Proton Shift (ppm) No. of Protons	Carbon Shift (ppm)	HMBC (ppm)
C3	0.99, 3H, doublet, $J_{3,2}$ = 6.0 Hz	17.79	57.83, 58.92
C3′	1.01, 3H, doublet, $J_{3',2'}$ =6.2 Hz	19.61	42.92, 56.16, 137.30
N-CH_3	2.350, 3H, singlet	33.93	57.83
N′-CH_3	2.356, 3H, singlet	33.86	56.16
C1′	2.54, 1H, multiplet 2.63, 1H, multiplet	42.92	19.61, 56.16, 129.38, 137.30
C2′	2.72, 1H, multiplet $J_{2',3'}$ = 6.2 Hz	56.16	19.61, 33.86, 42.92, 129.39, 137.30
C2	3.31, 1H, multiplet $J_{2,1}$ = 10.2 Hz, $J_{2,3}$ = 6.1 Hz	57.83	17.79, 33.93, 58.92, 141.02, 142.70
C1	3.70, 1H, doublet $J_{1,2}$ = 10.2 Hz	58.92	17.79, 57.83, 128.07, 128.14, 141.02, 142.70
Ar-$C_{3',5'}$	7.06, 2H, doublet	129.39	42.92, 126.59, 141.02
Ar-$C_{2',6'}$	7.20, 2H, doublet	128.14	58.92, 129.39, 137.30
Ar-C_4	7.18, 1H, multiplet	126.59	128.07, 128.79, 142.70
Ar-$C_{3,5}$	7.29, 2H, multiplet	128.79	58.92, 126.59, 142.70
Ar-$C_{2,6}$	7.35, 2H, multiplet	128.07	58.92, 126.59, 142.70,
Ar-$C_{4'}$	–	137.30	–
Ar-$C_{1'}$	–	141.02	–
Ar-C_1	–	142.70	–

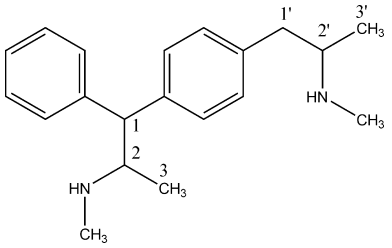


FIG. 9—*Structure of by-product 3.*

synthesis procedure for making "didesoxyephedrine" (14). This reaction was conducted several times; however, it failed to produce *N, N′*-dimethyl-3,4-diphenylhexane-2,5-diamine. When the reaction mixture was heated with dilute acetic acid for several hours at 80°C, a number of compounds having a molecular weight similar to that of a methylamphetamine dimer were formed, one of which was *N, N′*-dimethyl-3,4-diphenylhexane-2,5-diamine. It is believed Gero most likely formed the dimer(s) during the steam distillation step and not before. Whether Gero formed and isolated the dimer *N, N′*-dimethyl-3,4-diphenylhexane-2,5-diamine cannot be confirmed. Furthermore, it cannot be confirmed if Emde isolated only one or a mixture of the methylamphetamine dimer by-products identified in this article (13).

Gero provides an argument for the formation of this methylamphetamine dimer as being a result of dimerization of an intermediate mono-radical that forms during the reaction (Fig. 12) (14). He bases his theory on the fact that hydrogen can break the highly polar C–Cl bond, which then forms a mono-radical at the benzylic carbon. This mono-radical then reacts quickly with either a hydrogen atom to form methylamphetamine or with another mono-radical to form the dimer molecule (14). From this, we can postulate a

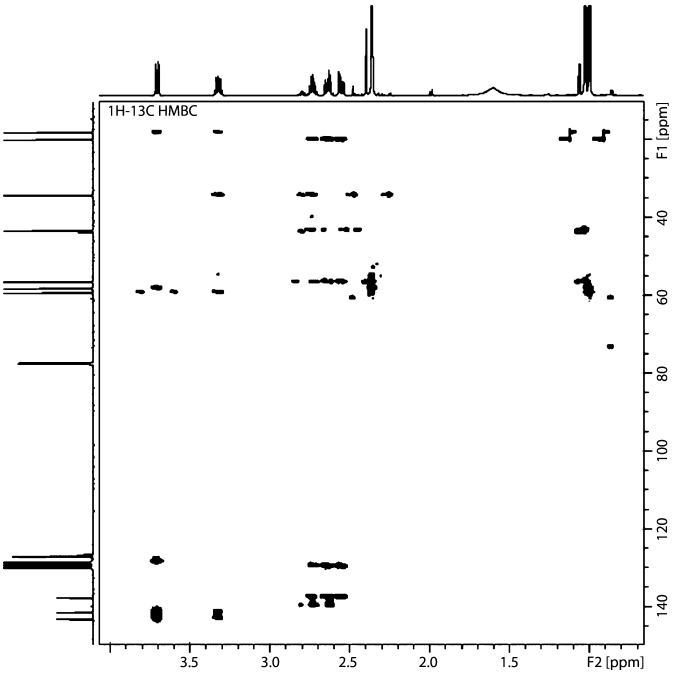


FIG. 11—*HMBC of by-product 3.*

tentative mechanism for the formation of by-products 1, 2, and 3 (Figs. 13 and 14).

Conclusions

The structures of three by-products repeatedly detected in methylamphetamine prepared via the "Emde" method have been

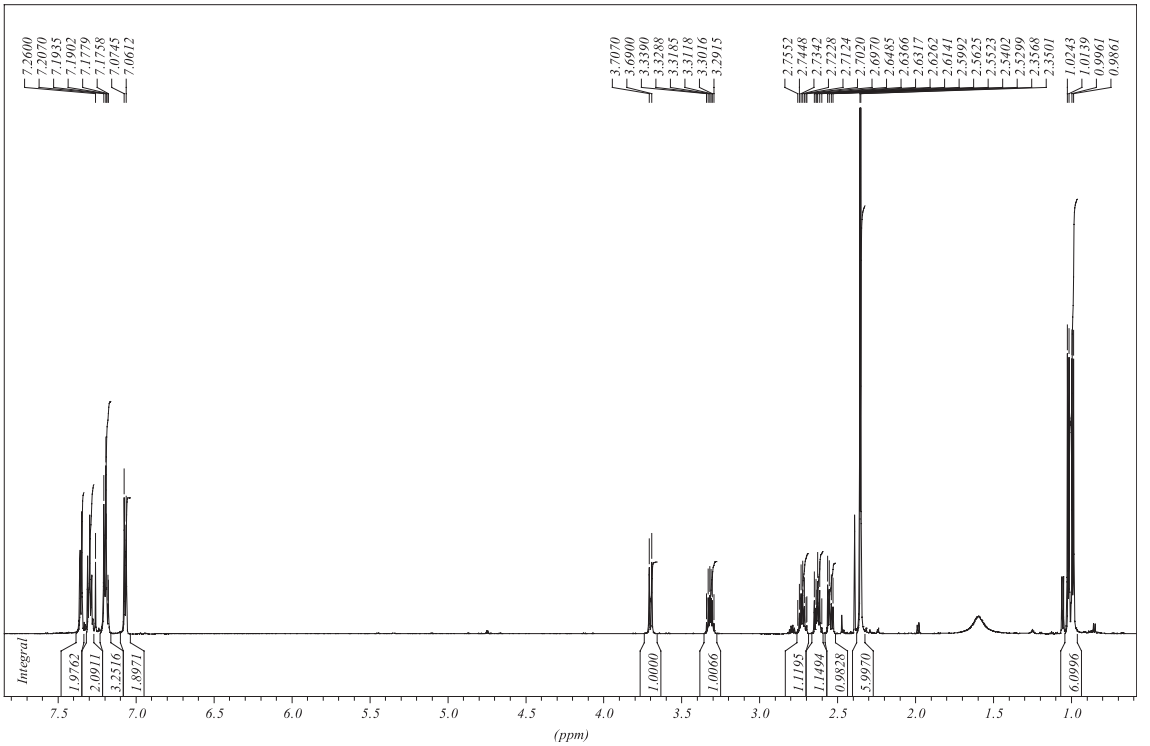


FIG. 10—*^{1}H NMR of by-product 3.*

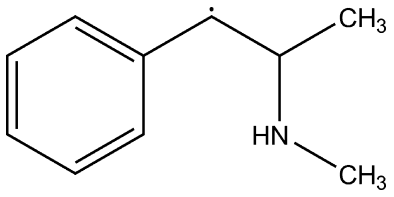


FIG. 12—*Mono-radical of methylamphetamine.*

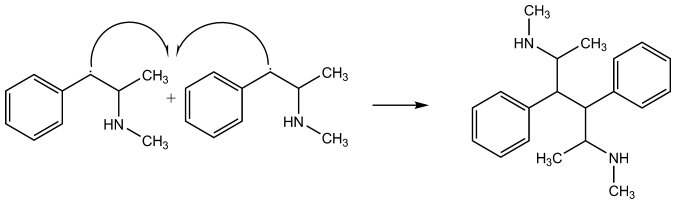


FIG. 13—*Tentative mechanism for the formation of by-product 1 and by-product 2.*

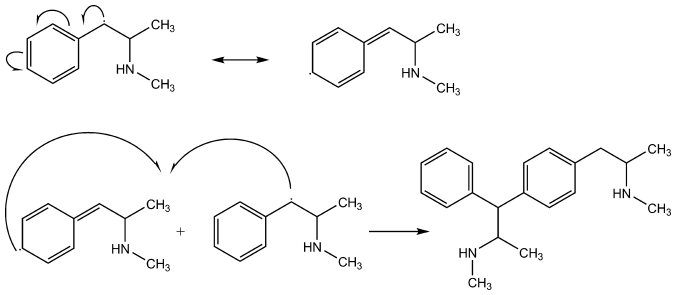


FIG. 14—*Tentative mechanism for the formation of by-product 3.*

determined as (2*S*,3*S*,4*S*,5*S*) or (2*S*,3*R*,4*R*,5*S*)—*N, N*′-dimethyl-3,4-diphenylhexane-2,5-diamine, (2*S*,3*S*,4*R*,5*S*)—*N, N*′-dimethyl-3,4-diphenylhexane-2,5-diamine and *N*-methyl-1-{4-[2-(methylamino) propyl]phenyl}-1-phenylpropan-2-amine. *N*-methyl-1-{4-[2-(methylamino)propyl]phenyl}-1-phenylpropan-2-amine was detected in methylamphetamine prepared by synthetic routes other than the "Emde" procedure in the course of this work. It has also been reported in the literature as a compound present in methylamphetamine prepared by the "Nagai" and "Moscow" routes (16,17).

The other two compounds were not detected in methylamphetamine prepared by any of the other common synthetic approaches to methylamphetamine such as the various hydriodic acid reductions of ephedrine or pseudoephedrine. Detection of one or more of these by-products in the organic impurity profile of a methylamphetamine sample may suggest that the "Emde" route had been employed. However, confirmation by the other chemical profiling techniques should be conducted before any conclusions are drawn.

Acknowledgments

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References

1. United Nations Office on Drugs and Crime. World drug report 2007, http://www.unodc.org/unodc/en/data-and-analysis/WDR-2007.html Accessed November 1, 2008.
2. Allen A, Cantrell TS. Synthetic reductions in clandestine amphetamine and methamphetamine laboratories: a review. Forensic Sci Int 1989;42:183–99.
3. Remberg B, Stead AH. Drug characterization/impurity profiling, with special focus on methamphetamine: recent work of the United Nations International Drug Control Programme. Bull Narc 1999;51:97–117.
4. Allen CA, Kiser WO. Methamphetamine from ephedrine: 1. Chloroephedrines and aziridines. J Forensic Sci 1987;32:953–62.
5. Skinner HF. Methamphetamine synthesis via hydriodic acid/red phosphorus reduction of ephedrine. Forensic Sci Int 1990;48:123–34.
6. Cantrell TS, John B, Johnson L, Allen AC. A study of impurities found in methamphetamine synthesized from ephedrine. Forensic Sci Int 1988;39:39–53.
7. Windahl KL, McTigue MJ, Pearson JR, Pratt SJ, Rowe JE, Sear EM. Investigation of the impurities found in methamphetamine synthesised from pseudoephedrine by reduction with hydriodic acid and red phosphorus. Forensic Sci Int 1995;76:97–114.
8. Skinner HF. Methamphetamine synthesis via reductive alkylation hydrogenolysis of phenyl-2-propanone with *N*-benzylmethylamine. Forensic Sci Int 1993;60:155–62.
9. Lambrechts M, Klemetsrud T, Rasmussen KE, Storesund HJ. Analysis of Leuckart-specific impurities in amphetamine and methamphetamine. J Chromatogr 1984;284:499–502.
10. Barron RP, Kruegel AV, Moore JM, Kram TC. Identification of impurities in illicit methamphetamine samples. J Assoc Off Anal Chem 1974;57:1147–58.
11. Kram TC, Kruegel AV. The identification of impurities in illicit methamphetamine exhibits by gas chromatography/mass spectrometry and nuclear magnetic resonance spectroscopy. J Forensic Sci 1977;22:40–52.
12. Salouros H, Collins M, Tarrant G, George AV. *N*-Cyanomethyl-*N*-methyl-1-(3′,4′-methylenedioxyphenyl)-2-propylamine: an MDMA manufacturing by-product. J Forensic Sci 2008;53:1083–91.
13. Emde H. Concerning diastereoisomers. I. Configuration of ephedrine; II. Steric inversion of ephedrine with hydrochloric acid; III. Chloro- and bromo-ephedrine, IV Steric inversion of ephedrine with sulfuric acid. Helv Chim Acta 1929;12:365–405.
14. Gero A. Some reactions of 1-phenyl-1chloro-2-methylaminopropane. I. Reactions with metals and with hydrogen. J Org Chem 1951;16:1731–5.
15. National Bureau of Investigation. Project SMT – CT98 – 2277, Development of a harmonised method for the profiling of amphetamine, Final Report, June 2003. Finland: National Bureau of Investigation, 2003.
16. Ko BJ, Suh S, Suh YJ, In MK, Kim SH. The impurity characteristics of methamphetamine synthesized by the Emde and Nagai method. Forensic Sci Int 2007;170:142–7.
17. Lee JS, Han EY, Lee SY, Kim EM, Park YH, Lim MA, et al. Analysis of the impurities in the methamphetamine synthesized by three different methods from ephedrine and pseudoephedrine. Forensic Sci Int 2006;161:209–15.
18. Silverstein RM, Webster FX, Kiemle DJ. Spectrometric identification of organic compounds, 7th edn. New Jersey: John Wiley & Sons, 2005.

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