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N-Cyanomethyl-*N*-Methyl-1-(3′,4′-methylenedioxyphenyl)-2-propylamine: An MDMA Manufacturing By-Product

ABSTRACT: This paper describes the structural elucidation of a compound produced during the synthesis of 3,4-methylenedioxymethylamphetamine (MDMA) via the reductive amination of 3,4-methylenedioxyphenyl-2-propanone (3,4-MDP-2-P) with methylamine and sodium cyanoborohydride. The compound was isolated from MDMA by column chromatography, proton and carbon nuclear magnetic resonance spectroscopy, LC/mass spectrometry, and total synthesis were used to identify the compound as *N*-cyanomethyl-*N*-methyl-1-(3′,4′-methylenedioxyphenyl)-2-propylamine. This compound has been identified as a potential synthetic route marker for the reductive amination of 3,4-MDP-2-P with methylamine and sodium cyanoborohydride and as such it should prove valuable to forensic scientists engaged in profiling illicit drugs. Profiling MDMA can provide useful information to law enforcement agencies relating to synthetic route, precursor chemicals and reagents employed and may be used for comparative analyses of different drug seizures. This paper also describes the structural elucidation of the analogous methylamphetamine synthetic route marker compound, *N*-cyanomethyl-*N*-methyl-1-phenyl-2-propylamine, produced during the reductive amination of phenyl-2-propanone using methylamine and sodium cyanoborohydride.

KEYWORDS: forensic science, chemical profiling, 3,4-methylenedioxymethylamphetamine, methylamphetamine, cyanoborohydride, *N*-cyanomethyl-*N*-methyl-1-(3′,4′-methylenedioxyphenyl)-2-propylamine, 2-(dimethylamino)-2-methyl-3-(3′,4′-methylenedioxyphenyl)-propanenitrile, *N*-cyanomethyl-*N*-methyl-1-phenyl-2-propylamine

"Ecstasy" or 3,4-methylenedioxymethylamphetamine (MDMA) is a major illicit drug of choice in many countries including the United States, the Netherlands, Germany, France, Italy, and Australia (1). In Australia, MDMA has been available for many years but since the late 1990s the number of border level seizures of MDMA powder and "Ecstasy" tablets has increased significantly, peaking at over 2000 kg in 2004/2005 (2).

3,4-Methylenedioxymethylamphetamine may be prepared via a variety of synthetic routes but the most common method currently in use is the reductive amination of 3,4-methylenedioxyphenyl-2-propanone (3,4-MDP-2-P) with methylamine (1). The 3,4-MDP-2-P is allowed to react with methylamine to form an imine which is then reduced to MDMA as shown in Fig. 1. The most common reducing agents encountered are sodium borohydride, an aluminum amalgam, or hydrogen gas with an appropriate catalyst such as platinum oxide (1). Each of these procedures is comparatively easy to perform and give good yields.

Another reducing agent, sodium cyanoborohydride may also be used. This method is effective, easy to use, and also gives very good yields. In a recent publication by Swist et al. on ecstasy synthesis methods, a tentative structural identification, shown in Fig. 2, was given for a compound that apparently only occurred in MDMA synthesized using cyanoborohydride as the reducing agent (3). The identification of this compound as 2-(dimethylamino)-2-methyl-3-(3,4-methylenedioxyphenyl)-propanenitrile (Fig. 2) was made on the basis of the mass spectral fragmentation pattern. The compound was recommended by Swist et al. (3) as a compound that could potentially indicate that reductive amination with methylamine and cyanoborohydride had been employed. Such marker compounds may be useful to forensic scientists engaged in profiling illicit drugs such as MDMA. While such profiling is unable to assist in determining the geographical region of manufacture, as is the case for cultivated drugs such as heroin and cocaine, it does produce valuable information on the synthetic route and precursor chemicals that were employed in manufacture. This is because the chemical reactions used to prepare these drugs generate by-products many of which are indicative of the synthetic route. It is rare that all such by-products are removed prior to illicit trafficking of the drugs (4,5). This paper describes the isolation of the compound tentatively identified by Swist et al. (3) as 2-(dimethylamino)-2-methyl-3-(3′,4′-methylenedioxyphenyl)-propanenitrile (Fig. 2). The structural elucidation of this compound as *N*-cyanomethyl-*N*-methyl-1-(3′,4′-methylenedioxyphenyl)-2-propylamine, shown in Fig. 6, by proton, carbon nuclear magnetic resonance (^{1}H NMR, ^{13}C NMR), and total synthesis is also described. Experiments showing that Swist's conclusion that this molecule is a marker compound for the cyanoborohydride route is correct are also described.

This paper also explores the synthesis of methylamphetamine from the reductive amination of phenyl-2-propanone (P2P) using methylamine and sodium cyanoborohydride. The structural elucidation of the analogous synthetic route marker compound, *N*-cyanomethyl-*N*-methyl-1-phenyl-2-propylamine, shown in Fig. 10, is also presented in this paper.

Experimental Section

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). The

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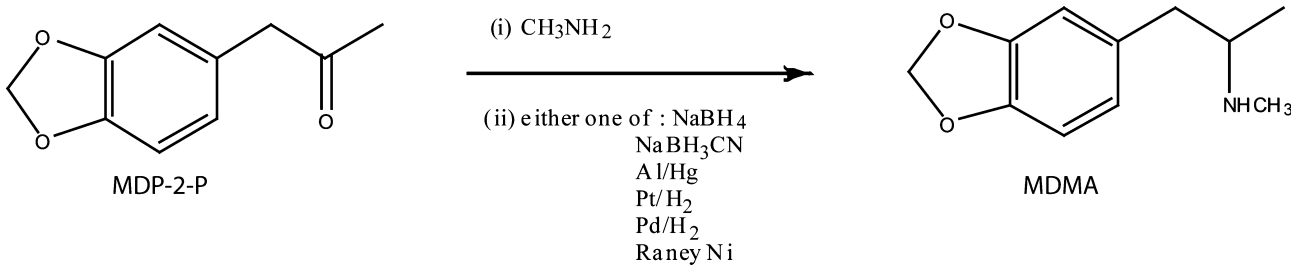
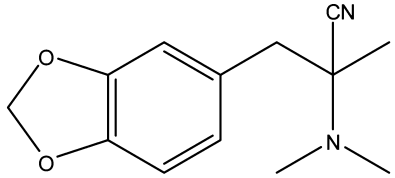


FIG. 1—*The reductive amination of 3,4-MDP-2-P to MDMA.*



2-(dimethylamino)-2-methyl-3-(3,4-methylenedioxyphenyl)-propanenitrile

FIG. 2—*Structure of manufacturing by-product as proposed by Swist et al. (3).*

precursors 3,4-MDP-2-P and P2P used in the synthesis of MDMA and methylamphetamine, respectively, were also obtained from the reference collection of the National Measurement Institute. Methylamine hydrochloride (98%), isopropanol, *n*-eicosane (99%), hexane, diethyl ether, and toluene were obtained from Merck (Kilsyth, Vic, Australia). Analytical grade methanol and dichloromethane were obtained from Mallinckrodt Chemicals (Philipsburg, NJ). Hydrochloric acid (36%), sodium hydroxide pellets, sodium carbonate, and acid washed sand were obtained from UNIVAR Ajax Finechem (Seven Hills, NSW, Australia). Chloroacetonitrile (99%) and silica gel (200–400 mesh 60Å) were obtained from Aldrich (Castle Hill, NSW, Australia); benzene from Riedel-deHaen (Seelze, Germany) and sodium cyanoborohydride from Fluka (Buchs SG, Switzerland). All reagents were used without further purification.

Reactions

Reactions 1: Synthesis of MDMA via Reductive Amination with Methylamine and Sodium Cyanoborohydride—3,4-Methylenedioxyphenyl-2-propanone was added to a solution of methylamine hydrochloride in methanol with stirring (6–8). Sodium cyanoborohydride was added with stirring over a period of 30 min. Stirring was continued for 36 h at room temperature and the reaction mixture was poured into acidified water. The mixture was washed with dichloromethane. The aqueous layer was basified to pH 12 with sodium hydroxide solution and MDMA base extracted with dichloromethane. The dichloromethane was removed using a rotary evaporator leaving MDMA base as oil. The oil was dissolved in cooled isopropanol and acidified with 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 MDMA hydrochloride.

Reactions 2: Synthesis of N-*Cyanomethyl*-N-*Methyl-1-(3′,4′-Methylenedioxyphenyl)-2-Propylamine*—This synthesis was based on the method of Quintilla (9). Sodium carbonate was added to a solution of chloroacetonitrile in benzene with stirring. To this solution, a mixture of MDMA in benzene was added in a drop wise manner. The mixture was refluxed for 14 h and allowed to cool. The reaction mixture was filtered and the solvent was removed using a rotary evaporator leaving *N*-cyanomethyl-*N*-methyl-1-(3′,4′-methylenedioxyphenyl)-2-propylamine as a yellow oil. The oil was distilled at 180°C at 0.8 mmHg.

Reactions 3: Synthesis of Methylamphetamine via Reductive Amination with Methylamine and Sodium Cyanoborohydride—The same procedure as outlined in Reactions 1 was followed in synthesizing methylamphetamine, only in this case P2P was used as the starting material (6–8).

Reactions 4: Synthesis of N-*Cyanomethyl*-N-*Methyl-1-Phenyl-2-Propylamine*—The method of Quintilla (9) was used. Sodium carbonate was added to a solution of chloroacetonitrile in benzene with stirring. To this solution, a mixture of methylamphetamine in benzene was added in a drop wise manner. The mixture was refluxed for 14 h and allowed to cool. The reaction mixture was filtered and the solvent was removed using a rotary evaporator leaving *N*-cyanomethyl-*N*-methyl-1-phenyl-2-propylamine as orange oil. The oil was distilled at 155°C at 0.8 mmHg.

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

Gas Chromatography/Mass Spectrometry

Gas chromatography–mass spectrometry (GC–MS) analyses were performed using an Agilent Technologies 6890N GC (Agilent J&W, Santa Clara, CA) interfaced to an Agilent 5973N mass selective detector. A 0.20 mm i.d. × 25 m, 0.33 μm DB-1MS column (Agilent) 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 amu was scanned. A 990 μL, single tapered, injection port liner with glass wool packing was employed for all injections.

Nuclear Magnetic Resonance Spectroscopy

All ^{1}H NMR and ^{13}C NMR were acquired on a Bruker DMX500 spectrometer (Bruker-Biospin, Rheinstetten, Germany) in $CDCl_3$. All ^{1}H NMR spectra were recorded in $CDCl_3$ at 300 K and referenced to the signal arising from residual $CHCl_3$ (7.26 ppm). The spectra were measured at 500 MHz, with a total number of 16 scans taken, a sweep width of 10 ppm, and a prescan delay of 20 sec. All ^{13}C NMR spectra were also recorded in $CDCl_3$ at 300 K and referenced on the central line of the $CDCl_3$ triplet

(77.0 ppm). The spectra were measured at 126 MHz, with a total number of 1196 scans taken, a sweep width of 259 ppm, and a pre-scan delay of 2 sec.

Electrospray Ionization/Mass Spectrometry

Electrospray ionization (ESI)/MS experiments were conducted on a Quattro Micromass with MassLynx V4.1 software (Waters, Milford, MA). The sample was dissolved in a methanol:water (1:1) mixture and analyzed by direct infusion at 5 μL/min. The mass scan range was 50–580 amu. Capillary voltage was set at 3.20 kV, cone voltage at 20 V, and the source temperature at 80°C. The multiplier voltage was set at 650 V.

Preparation of Phosphate Buffer

The buffer solution at pH 7.0 (0.066 M) was prepared by adding Na_2HPO_4 (5.557 g) and $NaH_2PO_4.2H_2O$ (4.157 g) with 1000 mL water.

Preparation of Internal Standard Solution

Eicosane internal standard solution (25 ppm) was prepared by dissolving *n*-eicosane (25 mg) in toluene (100 mL) then diluted 10-fold in toluene.

Sample Preparation for MDMA Profiling by GC–MS

3,4-Methylenedioxymethylamphetamine hydrochloride (100 mg) was dissolved in phosphate buffer (4 mL), vortexed for 10 sec, and placed on a Clements mixer (Crown Scientific, Moorebank, NSW, Australia) for 1 h. The sample was centrifuged at 2500 rpm for 8 min and filtered through 0.45-μm Teflon filter. Internal standard solution (100 μL) was added to the solution, which was then placed on the Clements mixer for 15 min. The solution was centrifuged at 2500 rpm for 8 min and the upper toluene layer was removed and analyzed by GC/MS.

Isolation of a Manufacturing By-Product of MDMA Synthesis

Silica gel was dry packed to form a 20 × 4 cm column. The silica gel was washed with 500 mL of diethyl ether:hexane (95:5) 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). MDMA hydrochloride (5.8 g), synthesized in Reactions 1, was converted to the free base and dissolved in the mobile phase (2 mL). This solution was added to the top of the column and the column was eluted with the mobile phase (50 mL) then fractions (10 mL each) were collected. Fifteen fractions were collected. GC/MS analysis of each fraction revealed fraction 5 through to fraction 11 as containing the manufacturing by-product. The fractions were combined and approximately 20 mg of the manufacturing by-product was recovered.

Results and Discussion

The MDMA hydrochloride synthesized according to the reductive amination procedure described in Reactions 1, which employed sodium cyanoborohydride as the reducing agent, was analyzed by GC/MS and the total ion chromatogram (TIC) is shown in Fig. 3*A*. The mass spectrum of the peak eluting at 12.90 min, shown in Fig. 3*B*, is due to MDMA. The identity of the product was confirmed by comparison to a certified reference standard. The mass

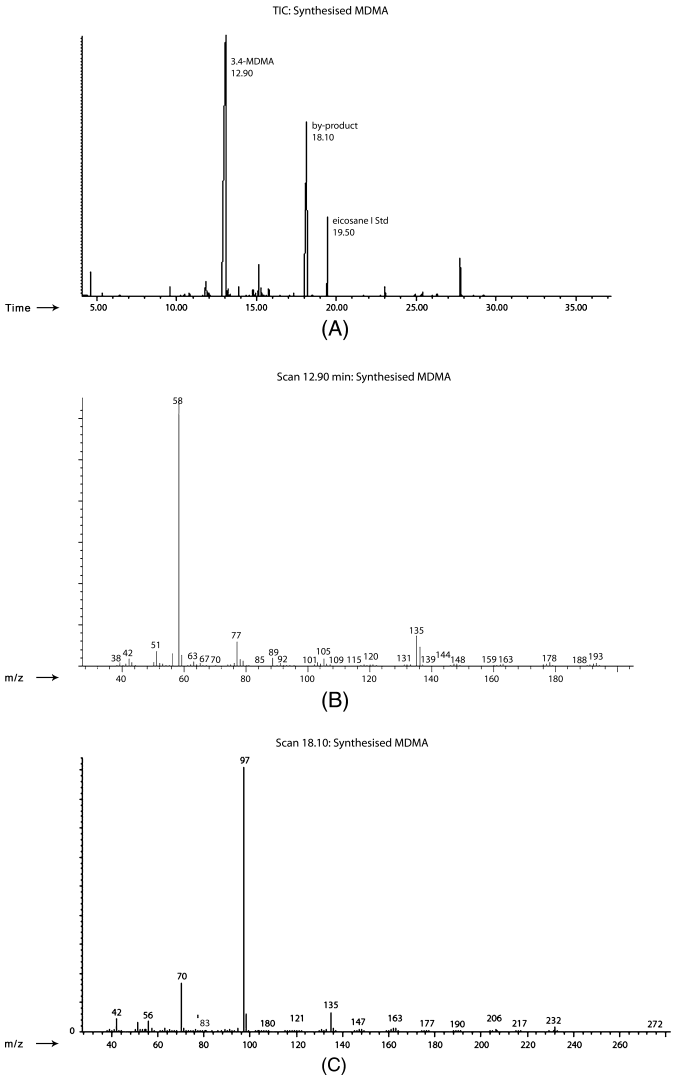


FIG. 3—*(A) TIC of MDMA product synthesized via reductive amination of 3,4-MDP-2-P with methylamine and using sodium cyanoborohydride; (B) mass spectrum of MDMA product synthesized via reductive amination of 3,4-MDP-2-P with methylamine and using sodium cyanoborohydride; (C) mass spectrum of the manufacturing by-product.*

spectrum of the manufacturing by-product represented by the chromatographic peak eluting at 18.10 min is depicted in Fig. 3*C*. This spectrum closely matches that described by Swist et al. (3) in which the by-product was tentatively identified as 2-(dimethylamino)-2-methyl-3-(3′,4′-methylenedioxyphenyl)-propanenitrile shown in Fig. 2. This tentative identification was based on the mass spectral fragmentation pattern (3). The mass spectral data reported for this unknown compound was *m/z* 97(100), 70 (16), 135 (5), and 232 (1) which is consistent with the mass spectrum of the chromatographic peak at 18.10 min shown in Fig. 3*C* (3). The apparent molecular weight was 232, which is also consistent with the structure suggested in the literature (3). Approximately 20 mg of the by-product was isolated by column chromatography for characterization. GC/MS analysis gave the TIC shown in Fig. 4*A*. The mass spectrum of the peak eluting at 18.10 min is shown in Fig. 4*B*. This spectrum matches the mass spectrum of the peak eluting at 18.10 min in Fig. 3*C*, confirming that the desired impurity had been isolated from the reaction mixture. ESI/MS confirmed the molecular weight as 232.2 with *m/z* values of 233 ($M + H^+$, 100), 194 (65), 163 (24).

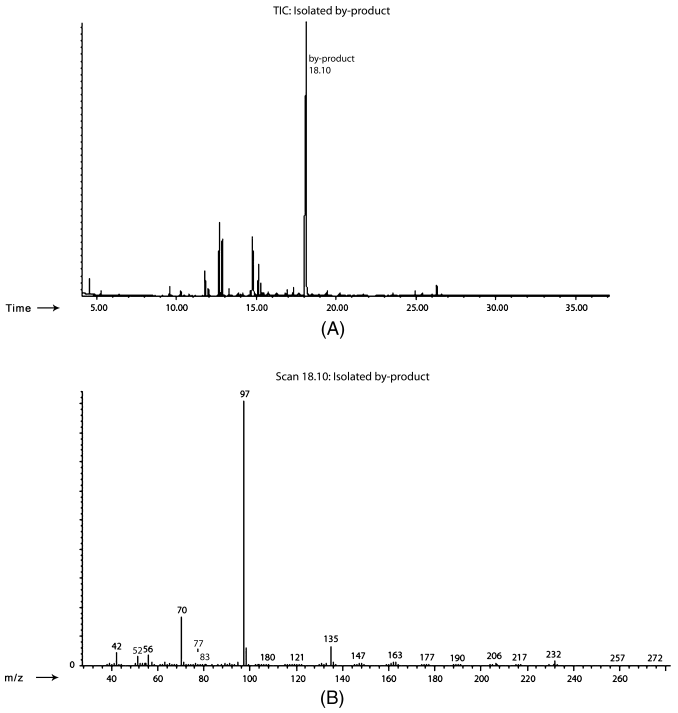


FIG. 4—*(A) TIC and (B) mass spectrum of the manufacturing by-product isolated from the MDMA synthesis described in Reactions 1 section.*

However, while the molecular weight agreed with the structure proposed in the literature (3) the ^{1}H NMR spectrum of the material isolated by column chromatography, shown in Fig. 5, did not. If the structure of the by-product was 2-(dimethylamino)-2-methyl-3-(3′,4′-methylenedioxyphenyl)-propanenitrile, then the ^{1}H NMR should display two singlets with one singlet integrating for three protons (the methyl group at position 2) and the other singlet integrating for six protons, assuming the two methyl groups attached to

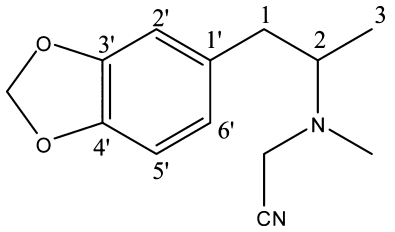


FIG. 6—*Structure of* N-*cyanomethyl*-N-*methyl-1-(3′,4′-methylenedioxyphenyl)-2-propylamine.*

the nitrogen atom are equivalent. There was only one singlet methyl group and one methyl group presenting as a doublet with a coupling constant of 6.52 Hz, consistent with $^{3}J_{CH3,\ H}$ in a freely rotating system. This is not consistent with the structure proposed in the literature (3) and shown in Fig. 2 but is consistent with *N*-cyanomethyl-*N*-methyl-1-(3′,4′-methylenedioxyphenyl)-2-propylamine as shown in Fig. 6. The data presented in Table 1 gives the assignments for the resonances obtained from the ^{1}H NMR spectrum. Complete structural elucidation of the compound was based on total synthesis of the molecule shown in Fig. 6 and 1D and 2D NMR experiments, including ^{1}H NMR, ^{13}C NMR, distortionless enhancement by polarization transfer (DEPT), heteronuclear single quantum coherence, and heteronuclear multiple bond coherence (HMBC).

The ^{1}H NMR spectrum (Fig. 5) confirmed the presence of 13 aliphatic protons. The doublet at δ 1.02 ppm integrating for three protons was assigned as the aliphatic methyl group at C3. The doublet of doublets at 2.38 ppm and integrating for one proton was assigned as one of the two benzylic protons at C1, and the multiplet at 2.87 ppm, integrating for one proton, was assigned as the second benzylic proton at C1. The multiplet at 2.86 ppm integrating for one proton was assigned as methine proton at C2. The singlet at δ 2.44 ppm integrating for three protons was assigned to the *N*-methyl group and the broad singlet at δ 3.55 ppm integrating for two protons was assigned to the N-CH_2-CN group. The singlet at

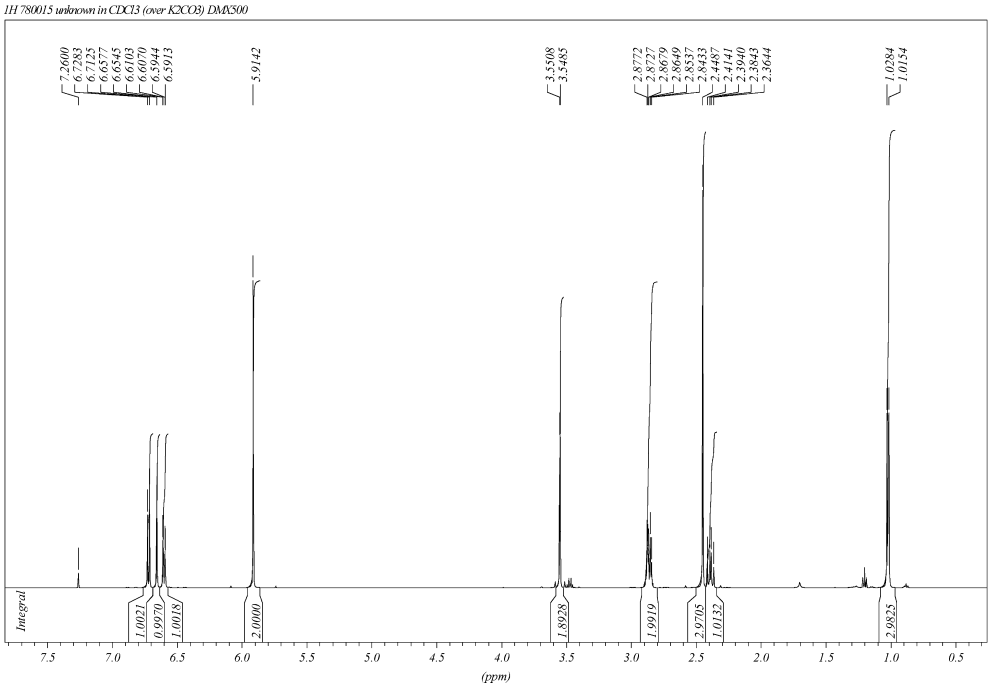
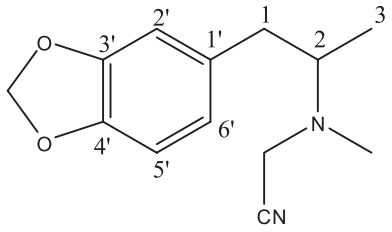


FIG. 5—*^{1}H NMR spectrum of the manufacturing by-product isolated from the MDMA synthesis described in Reactions 1 section.*

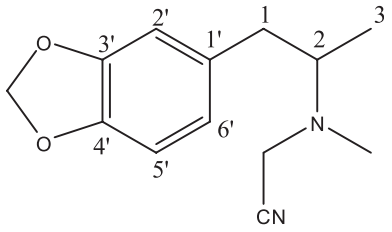
TABLE 1—*^{1}H NMR data obtained for the manufacturing by-product isolated by column chromatography.*



Chemical Shift (ppm)	Number of Protons	Assignment
1.02 (1.02)	3 protons, doublet, $^3J_{CH3,H}$ = 6.52 Hz	Ph-CH_2-CH-**CH_3**
2.38 (2.38)	1 proton, doublet of doublets, J_{gem} = 14.8 Hz, J_{vic} = 10.0 Hz	Ph-**CH_2**-CH-CH_3
2.44 (2.44)	3 protons, singlet	N-**CH_3**
2.86 (2.86)	1 proton, multiplet	Ph-CH_2-C**H**-CH_3
2.87 (2.87)	1 proton, multiplet	Ph-**CH_2**-CH-CH_3
3.55 (3.55)	2 proton, broad singlet	N-**CH_2**-CN
5.91 (5.91)	2 protons, singlet	O-**CH_2**-O
6.65 (6.65)	1 proton, doublet, $^3J_{H2,H6}$ = 1.59 Hz	Ar-**H_2**
6.71 (6.71)	1 proton, doublet, $^3J_{H5,H6}$ = 7.86 Hz	Ar-**H_5**
6.60 (6.60)	1 proton, doublet of doublets	Ar-**H_6**

The bracketed figures represent the ^{1}H NMR resonances for the synthesized *N*-cyanomethyl-*N*-methyl-1-(3′,4′-methylenedioxyphenyl)-2-propylamine. ^{1}H NMR, proton nuclear magnetic resonance spectroscopy.

TABLE 2—*^{13}C NMR data obtained for* N-*cyanomethyl*-N-*methyl-1-(3′,4′-methylenedioxyphenyl)-2-propylamine.*



Chemical Shift (ppm)	Assignment
15.11	Methyl group, position 3 (Ph-CH_2-CH-**CH_3**)
39.81	Benzylic carbon at position 1
37.78	-N-**CH_3**
60.10	Ph-CH_2-**CH**-CH_3 at position 2
42.40	-N-**CH_2**-CN
100.76	Methylenedioxy group (-O-**CH_2**-O-)
121.96	Ar-**$C_{6'}$**
109.38	Ar-**$C_{2'}$**
108.06	Ar-**$C_{5'}$**
133.01	Ar-**$C_{1'}$**
145.87	Ar-**$C_{3'}$** or Ar-**$C_{4'}$**
147.52	Ar-**$C_{3'}$** or Ar-**$C_{4'}$**
116.50	-CH_2-**C** ≡ N

^{13}C NMR, carbon nuclear magnetic resonance spectroscopy.

5.91 integrating for two protons was assigned as the methylenedioxy group. The coupling patterns observed at δ 6.59–6.72 ppm of the aromatic protons is typical of a 1, 3, 4-trisubstituted phenyl group. The resonance at 6.60 ppm is a doublet of doublets, integrating as one proton, is due to Ar-H_6. The large doublet (7.86 Hz) is the $^3J_{H5',H6'}$ consistent with an aromatic ortho coupling. The smaller coupling (1.59 Hz) is due to the meta coupling $^4J_{H2',H6'}$. The doublet (1.59 Hz) at 6.65 ppm is due to $H_{2'}$ and the doublet at 6.72 ppm is due to $H_{5'}$. This pattern combined with the presence of the methylenedioxy protons is diagnostic of a 3,4-methylenedioxyphenyl group.

The ^{13}C NMR spectral assignments are given in Table 2 and confirm the presence of six aliphatic carbons at δ 15.11, 37.78, 39.81, 42.40, 60.10, and 100.76 ppm and six aromatic carbons at δ 108.06, 109.38, 121.96, 133.01, 145.87, and 147.52 ppm with the resonance at δ 116.50 ppm being consistent with a nitrile group. DEPT experiments indicated the presence of three -CH_2- groups which is inconsistent with the structure shown in Fig. 2 but in agreement with the proposed structure depicted in Fig. 6.

The results of the HMBC spectrum, shown in Fig. 7 and Table 3, revealed a strong correlation of the protons at δ 2.38, 2.87 ppm and the three aromatic carbons at 1′, 2′, and 6′. This confirms that the resonances at δ 2.38 and 2.87 ppm are due to the benzylic protons. Table 3 also displays the strong correlation between the protons of the -N-CH_2-CN moiety at δ 3.55 ppm and the carbon atom at position 2 (60.10), the nitrile carbon (116.50), and *N*-methyl group (37.78), which is in agreement with the proposed structure.

N-cyanomethyl-*N*-methyl-1-(3′,4′-methylenedioxyphenyl)-2-propylamine (Fig. 6) was synthesized using a procedure shown in Fig. 8*A*. This synthetic route is analogous to that described by Quintella (9) where methylamphetamine instead of MDMA is used as the starting material (Fig. 8*B*). The TIC and mass spectrum of the synthesized material is shown in Figs. 9*A* and *B*, respectively. The mass spectrum of the chromatographic peak eluting at 18.10 min matches the spectrum of the isolated manufacturing by-

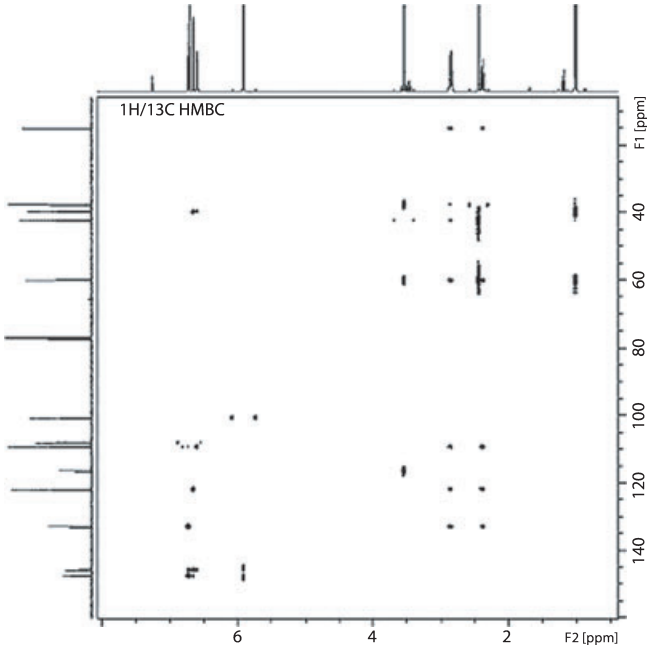
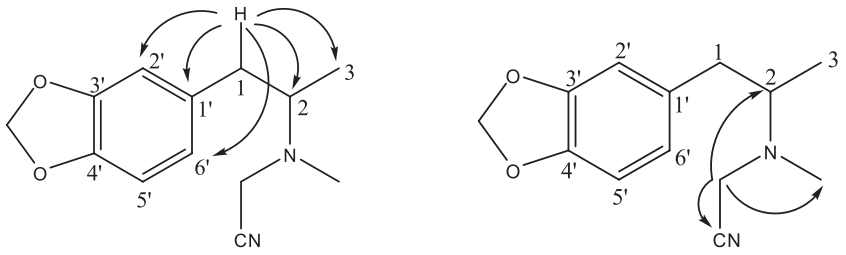


FIG. 7—*HMBC of the manufacturing by-product isolated from the MDMA synthesis described in Reactions 1 section.*

product shown in Fig. 4. The ^{1}H NMR spectrum of the synthesized material matched that of the material isolated from the MDMA reaction mixture by column chromatography. The proton resonances for the synthetic substance are listed in brackets in Table 1. The characterization data for the compound is as follows: found C 67.03%, H 7.05%, N 12.23%. $C_{13}H_{16}N_2O_2$ requires C 67.22%, H 6.94%, N 12.06%. υ_{max} (KBr)/cm^{-1} 2970, 2936, 2889, 2229, 1608, 1500, 1490, 1442, 1248, 1190, 1124, 1099, 1038, 928, 855, 810, 787, 605. δ_H (500 MHz, $CDCl_3$) 6.60–6.71 (3 H, m), 5.91 (2 H, s), 3.55 (2 H, s), 2.87 (1 H, m), 2.86 (1 H, m), 2.44 (3 H, s), 2.38

TABLE 3—*^{1}H NMR, ^{13}C NMR, and HMBC data obtained for* N-*cyanomethyl*-N-*methyl-1-(3′,4′-methylenedioxyphenyl)-2-propylamine.*



Assignment	Proton Shift (ppm)	Carbon Shift (ppm)	HMBC
3	1.02	15.11	39.81, 60.10
1	2.38, 2.87	39.81	15.11, 60.10, 109.38, 121.96, 133.01
N-**CH_3**	2.44	37.78	42.40, 60.10
2	2.86	60.10	15.11, 37.78, 39.81, 42.40, 133.01
N-**CH_2**-CN	3.55	42.40	37.78, 60.10, 116.50
O-**CH_2**-O	5.91	100.76	145.87, 147.52
6′	6.60	121.96	39.81, 108.06, 109.38, 145.87
2′	6.65	109.38	39.81, 121.96, 145.87, 147.52
5′	6.72	108.06	121.96, 133.01, 145.87, 147.52
1′	–	133.01	–
3′ or 4′	–	147.52	–
3′ or 4′	–	145.87	–
C ≡ N	–	116.50	–

HMBC, heteronuclear multiple bond coherence. ^{1}H NMR and ^{13}C NMR, proton and carbon nuclear magnetic resonance spectroscopy.

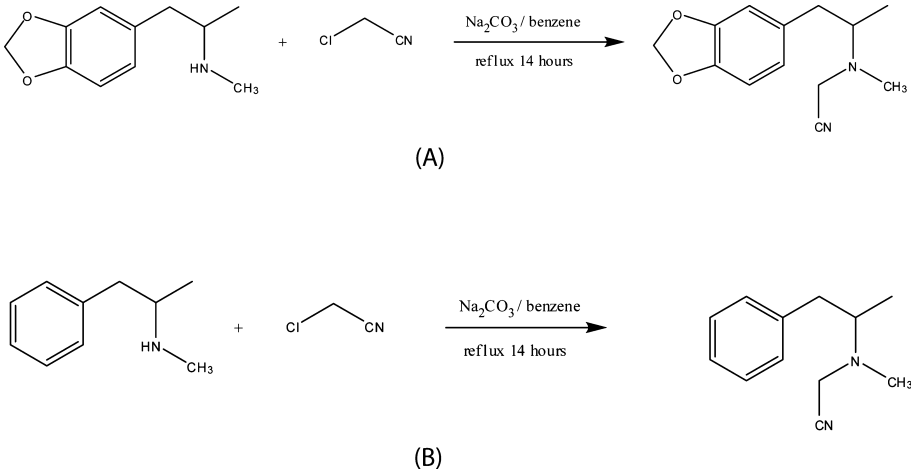


FIG. 8—*(A) Synthesis of* N-*cyanomethyl*-N-*methyl-1-(3′,4′-methylenedioxyphenyl)-2-propylamine and (B)* N-*cyanomethyl*-N-*methyl-1-phenyl-2-propylamine as outlined by Quintilla.*

(1 H, dd), 1.02 (3 H, d). δ_C (125 MHz, $CDCl_3$) 147.52, 145.87, 133.01, 121.96, 116.50, 109.38, 108.06, 100.76, 60.10, 42.40, 39.81, 37.78, 15.11. *m/z* (GC/MS) 97(100), 70 (19), 135 (7), and 232 (2).

It is evident from the proton and carbon NMR experiments and the synthetic experiments that the substance isolated from the MDMA reaction mixtures produced by cyanoborohydride reductive amination is the compound whose structure is shown in Fig. 6. A total of 13 reductive aminations of 3,4-MDP-2-P with methylamine using sodium cyanoborohydride were conducted in our laboratory. Each synthesis produced *N*-cyanomethyl-*N*-methyl-1-(3′,4′-methylenedioxyphenyl)-2-propylamine, the impurity represented by the chromatographic peak at 18.10 min shown in Fig. 3*A*. In five instances, the synthesis was conducted as outlined in Reactions 1. In the remaining eight cases, various changes were made to reaction conditions such as stoichiometry, reaction time, temperature, etc. In each of the 13 reactions, the by-product represented by the chromatographic peak at 18.10 min in Fig. 3 and subsequently identified as *N*-cyanomethyl-*N*-methyl-1-(3′,4′-methylenedioxyphenyl)-2-propylamine was observed. Furthermore, in the eight cases where reaction conditions were changed there was no apparent change observed in the relative amount of the impurity produced in these MDMA samples. Reductive amination of 3,4-MDP-2-P was then performed sixteen times using the mercury amalgam procedure, five times using the platinum/hydrogen method, and six times using sodium borohydride as the reducing agent. The by-product, *N*-cyanomethyl-*N*-methyl-1-(3′,4′-methylenedioxyphenyl)-2-propylamine, was not detected in the MDMA produced in any of these experiments. Swist et al. (3) suggested that the compound tentatively identified by them as the structure shown in Fig. 2, is a synthetic route marker compound for the reductive amination of 3,4-MDP-2-P with methylamine and sodium

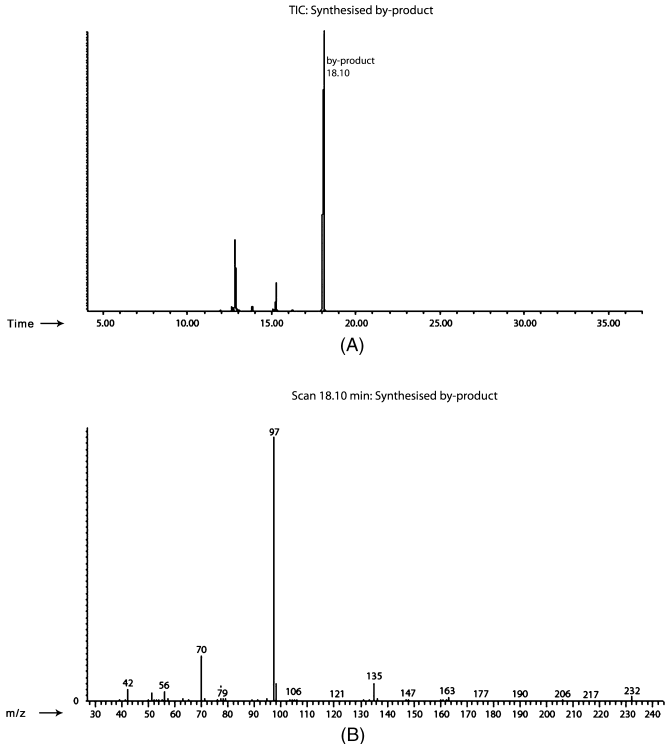


FIG. 9—*(A) TIC and (B) mass spectrum of synthesized* N-*cyanomethyl*-N-*methyl-1-(3′,4′-methylenedioxyphenyl)-2-propylamine.*

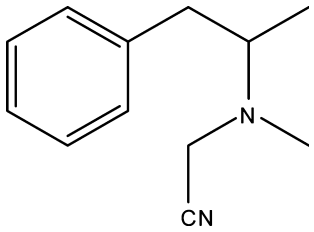


FIG. 10—*Structure of* N-*cyanomethyl*-N-*methyl-1-phenyl-2-propylamine.*

cyanoborohydride. This compound has now been identified in this work as *N*-cyanomethyl-*N*-methyl-1-(3′,4′-methylenedioxyphenyl)-2-propylamine (Fig. 6). Subsequent reductive amination experiments using cyanoborohydride and screening for the compound shown in Fig. 6 confirm Swist's suggestion that the compound is indeed a route marker.

If reductive amination of 3,4-MDP-2-P with methylamine and cyanoborohydride produced as a by-product the molecule shown in Fig. 6, it is logical that reductive amination of P-2-P under the same conditions should produce the analogous by-product shown in Fig. 10. Methylamphetamine was synthesized from P-2-P, methylamine, and sodium cyanoborohydride as outlined in Reactions 3 and analyzed by GC/MS. The TIC is shown in Fig. 11*A*. The major peak eluting at 6.7 min is due to the methylamphetamine. The identity of the product was confirmed by comparison to a certified reference standard.

The mass spectrum of the manufacturing by-product represented by the chromatographic peak eluting at 13.6 min is depicted in Fig. 11*B*. The mass fragmentation pattern of the by-product is consistent with the proposed structure *N*-cyanomethyl-*N*-methyl-1-

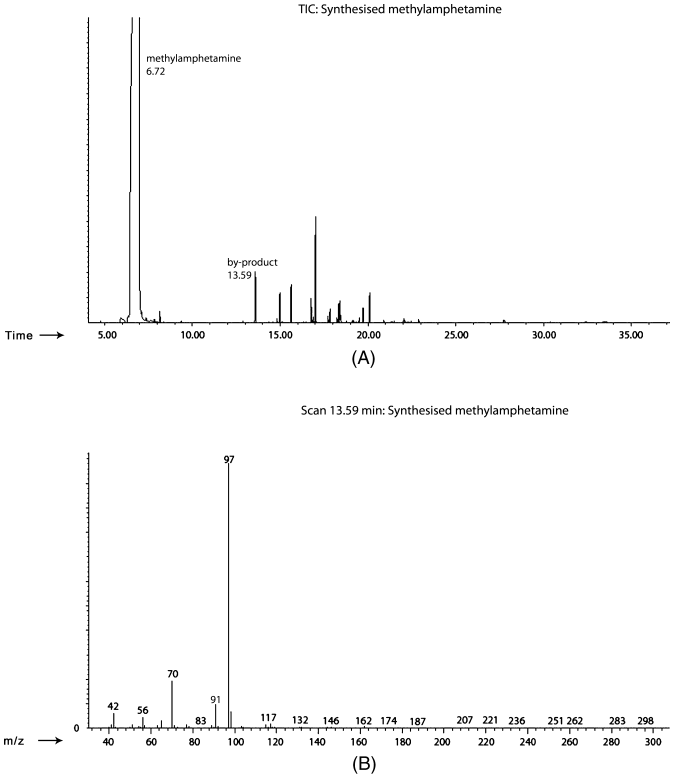


FIG. 11—*(A) TIC of methylamphetamine product synthesized via reductive amination of P-2-P with methylamine and using sodium cyanoborohydride; (B) mass spectrum of the manufacturing by-product.*

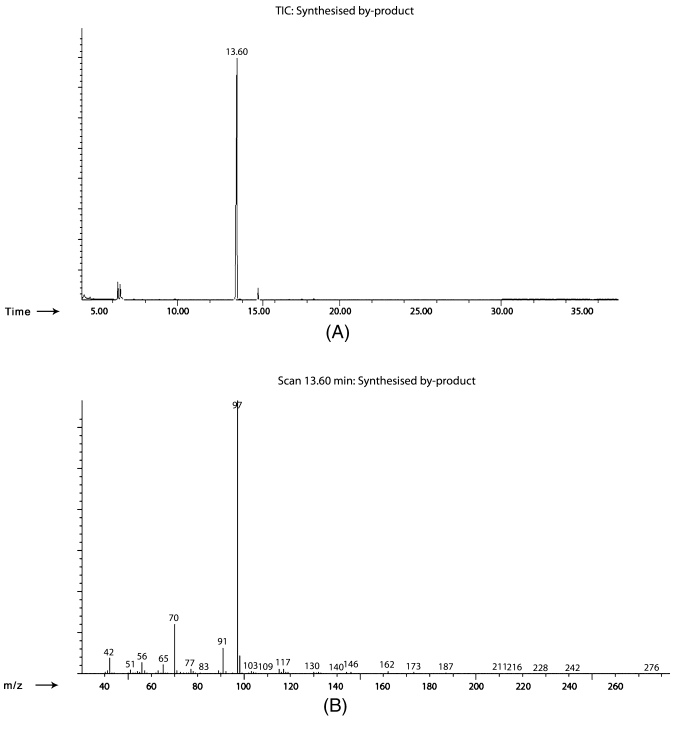
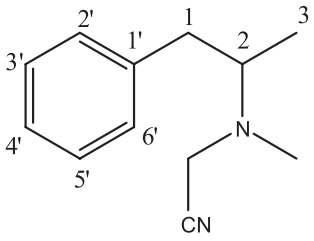


FIG. 12—*(A) TIC and (B) mass spectrum of synthesized* N-*cyanomethyl*-N-*methyl-1-phenyl-2-propylamine.*

phenyl-2-propylamine (Fig. 10). The by-product was synthesized using the procedure described by Quintella (9) shown in Fig. 8*B*. The TIC and mass spectrum of the synthesized material is shown

TABLE 4—*^{1}H NMR and ^{13}C NMR data obtained for* N-*cyanomethyl*-N-*methyl-1-phenyl-2-propylamine.*



Assignment	Proton Shift (ppm)	Number of Protons	Carbon Shift (ppm)
3	1.02	3 protons, doublet	15.19
1	2.46	1 protons, doublet of doublet	40.10
	2.97	1 proton, mulitplet	
N-**CH$_3$**	2.47	3 protons, singlet	37.83
2	2.92	1 proton, mulitplet	60.04
N-**CH$_2$**-CN	3.56	2 protons, singlet	42.40
1′	7.15–7.31	5 protons	139.30
2′ and 6′			129.12
3′ and 5′			128.32
4′			126.15
C ≡ N	–	–	116.58

^{1}H NMR and ^{13}C NMR, proton and carbon nuclear magnetic resonance spectroscopy.

in Figs. 12*A* and *B*, respectively. Both the retention time and mass spectrum of the chromatographic peak at 13.6 min match the retention time and mass spectrum of the manufacturing by-product shown in Figs. 11*A* and *B*. The synthesized *N*-cyanomethyl-*N*-methyl-1-phenyl-2-propylamine was analyzed by ^{1}H and ^{13}C NMR and the results are given in Table 4. The NMR analyses are consistent with the proposed structure (Fig. 10). These results are also consistent with the NMR data obtained by Sekine and Nakahara (10), who identified the product as having the same structure shown in Fig. 10. The characterization data for the compound is as follows: υ_{max} (KBr)/cm^{-1} 2970, 2936, 2800, 2229, 1603, 1494, 1455, 1154, 1124. δ_H (500 MHz, $CDCl_3$) 7.15–7.31 (5 H, m), 3.56 (2 H, s), 2.97 (1 H, m), 2.92 (1 H, m), 2.47 (3 H, s), 2.46 (1 H, dd), 1.02 (3 H, d). δ_C (125 MHz, $CDCl_3$) 139.30, 129.12, 128.32, 126.15, 116.58, 60.04, 42.40, 40.10, 37.83, 15.19. *m/z* (GC/MS) 97 (100), 70 (17), 91 (9).

A tentative mechanism for the formation of the structure shown in Fig. 6 is given in Fig. 13. This suggested mechanism assumes that *N*-formyl-MDMA is present in the synthesized MDMA. This assumption is based on our observations that approximately 90% of MDMA samples that have been profiled in our laboratory have been found to contain trace amounts of *N*-formyl-MDMA. The presence of *N*-formyl-MDMA in samples of MDMA has long been thought to be route specific for the Leuckart procedure. While it is true that this compound is present in significant amounts in MDMA synthesized using the Leuckart procedure it is also present in MDMA prepared by other methods. The presence of *N*-formyl-MDMA in MDMA samples appears to be independent of the synthetic route employed (11,12). Similarly *N*-formyl-methylamphetamine has been observed in most samples of methylamphetamine profiled in this laboratory irrespective of the synthetic route employed. It is likely that the same tentative mechanism would explain the formation of the cyanomethyl by-product in methylamphetamine. Further work is being undertaken to confirm that this is the mechanism.

Conclusions

The structure of a molecule repeatedly detected in MDMA synthesized via the reductive amination of 3,4-MDP-2-P using methylamine and sodium cyanoborohydride has been determined as *N*-cyanomethyl-*N*-methyl-1-(3′,4′-methylenedioxyphenyl)-2-propylamine. It appears that this compound is formed as a manufacturing by-product only when cyanoborohydride is used as the hydrogen source. Reductive amination of 3,4-MDP-2-P using other common hydrogen sources failed to produce this compound as a by-product. Similarly, reductive amination of P-2-P using methylamine and sodium cyanoborohydride produced the analogous by-product, *N*-cyanomethyl-*N*-methyl-1-phenyl-2-propylamine. The presence of these compounds in organic impurity profiles of MDMA or methylamphetamine is a likely indicator that cyanoborohydride was used as the hydrogen source in a reductive amination of 3,4-MDP-2-P or P-2-P with methylamine.

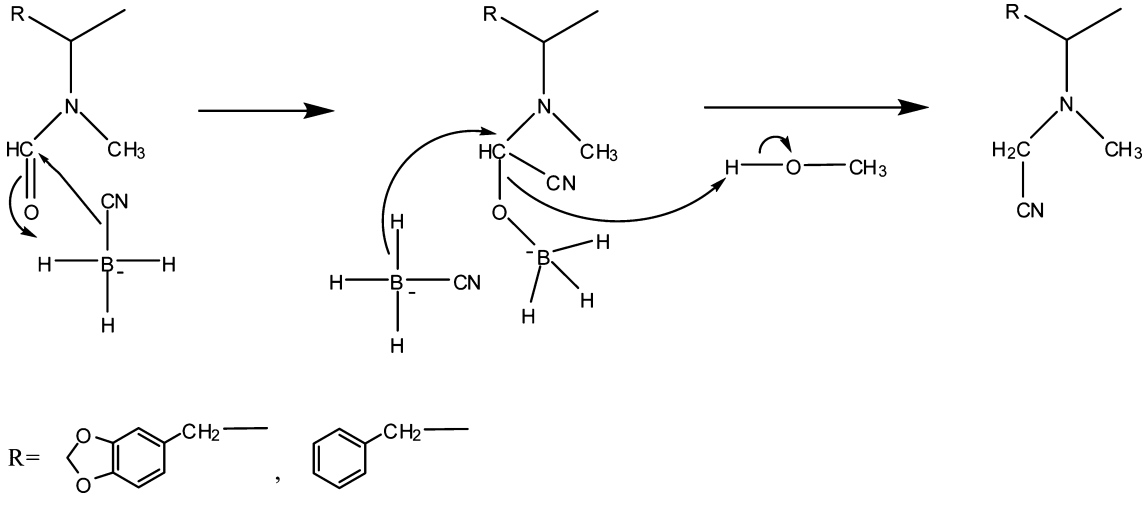


FIG. 13—*Tentative mechanism for the formation of* N-*cyanomethyl*-N-*methyl-1-(3′,4′-methylenedioxyphenyl)-2-propylamine and* N-*cyanomethyl*-N-*methyl-1-phenyl-2-propylamine.*

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