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Abuse of Smoking Methamphetamine Mixed with Tobacco: I. Inhalation Efficiency and Pyrolysis Products of Methamphetamine

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ABSTRACT: Experiments of smoking methamphetamine in tobacco have been investigated. Inhalation efficiencies of methamphetamine into tar were 6 to 17% according to the additive amounts, suction volume, and intervals of smoking. Major pyrolysis products of methamphetamine in tar were identified as methamphetamine, amphetamine, phenylacetone, dimethylamphetamine, *N*-formyl-, *N*-acetyl-, *N*-propionyl-, and *N*-cyanomethyl-methamphetamine by the spectral analysis of infrared spectra (IR), mass spectra (MS), and proton magnetic resonance spectra (PMR), and comparison with the samples synthesized from authentic samples by one step. The largest pyrolysis product was *N*-cyanomethylmethamphetamine which is a new compound and easily metabolized to methamphetamine in the body. Methamphetamine itself transferred into tar was not so large, but the total active compounds in tar which would be metabolized to methamphetamine in the body were considerably larger.

KEYWORDS: toxicology, methamphetamine, tobacco, pyrolysis, drug abuse, smoking experiment, pyrolysis products

In the last decade, abuse of methamphetamine has been the most serious drug problem in Japan. Methamphetamine has been abused mainly by intravenous or subcutaneous injection and partly by taking it orally or nasal inhalation [*1*]. In recent years, abuse of methamphetamine by smoking has appeared in Japan. These abusers inhale methamphetamine by smoking a cigarette mixed with it. Very little is known of how much methamphetamine is inhaled into the body by smoking and what kinds of pyrolysis products are produced by smoking it with tobacco.

The present paper describes the experiments of smoking methamphetamine in a cigarette and the identification of its pyrolysis products produced by smoking methamphetamine with tobacco.

Experimental Procedures

Chemicals

Methamphetamine hydrochloride (HCl) was purchased from Dainippon Pharmaceutical Co. Methylephedrine HCl and amphetamine sulfate were purchased from Yamada Pharma-

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ceutical Co. and Takeda Pharmaceutical Co., respectively. All reagents used in this study were analytical grade. All solvents were distilled before use.

Smoking Experiments

The smoking apparatus used in this study is shown in Fig. 1. "Peace" (70- by 8-mm inner diameter [ID], Japan Tobacco Inc.), a nonfilter cigarette, and "MILD SEVEN" (80- by 8-mm ID, Japan Tobacco Inc.), a filter cigarette, were used for the experiment. The tar formed by smoking was collected on a TOYO GA 200 glass fiber filter (45-mm ID). A standard smoking experiment was carried out by 35-mL puffs (2 s) at 60-s intervals. One cigarette was puffed an average of ten times leaving butts of 20 mm of a nonfilter cigarette and 30 mm of a filter cigarette.

The collected tar was dissolved in 50 mL of methanol, which is named tar extract. Methamphetamine that remained in butts and filters was extracted with 25 mL of methanol. It was confirmed that very little methamphetamine passed through the glass filter.

Analytical Procedures

Gas chromatography (GC) was carried out with a Shimazu 6APTF gas chromatograph with a flame ionization detector and a printer-plotter data system. A 2-cm by 3-mm ID glass column packed with 10% apiezon grease L and 5% potassium hydroxide on chromosorb W acid-washed dimethyldichlorosilane (AW-DMCS) 60–80 mesh was used for analysis. The column temperature was 175°C, detector and injection port temperature were 190°C, and the nitrogen carrier gas flow rate was at 90 mL/min.

Electron impact (EI) mass spectra (MS) at 70 eV were obtained using a Shimazu QP-1000 GC-mass spectrometer (GC/MS) and chemical ionization (CI) mass spectrometry at 100 eV using isobutane as a reagent gas was carried out with a Hitachi M-80 GC/MS. The GC/MS column was the same as the GC column mentioned above; column temperature was raised from 80 to 210°C at 10°C/min. Its initial hold time was 1 min and its final hold time 20 min. Carrier gas was helium and flow rate was at 30 mL/min.

Infrared spectra (IR) were recorded on a Shimazu IR-420 infrared spectrophotometer. The proton magnetic resonance (PMR) spectra were obtained in deuterochloroform with a JEOL JNM-GX270(270MHz) and a Varian EM-360(60MHz).

Calibration Curve—Quantitative analysis of methamphetamine by GC was performed by the method described in our previous paper [2] as follows. Each 1 mL of methanol solutions

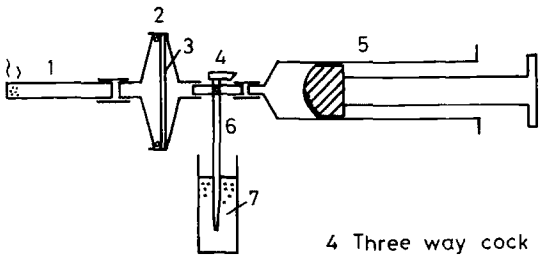


FIG. 1—*Smoking apparatus.*

containing 2, 5, 20, 50, and 100 μg/mL of methamphetamine HCl was put in a 5-mL test tube and a drop of concentrated hydrochloric acid was added into the solution, followed by the evaporation of the solution under nitrogen stream. One millilitre of hexane containing 40 μg/mL of biphenyl as an internal standard and two drops of concentrated ammonium hydroxide were added into the residue, followed by shaking and centrifugation. Five microlitres of the hexane layer were injected into a GC. The calibration curve was linear ($y = 64.5x + 0.57$, $\gamma = 0.9998$).

Isolation and Identification of Pyrolysis Products

To 50 mL of the tar extract were added a few millilitres of concentrated hydrochloric acid and condensed to a few millilitres under a reduced pressure. The condensed solution was washed with 2 mL of hexane three times, basified with concentrated ammonium hydroxide, and extracted with 2 mL of ether three times. The combined ether extract was dried over anhydrous sodium sulfate and evaporated to dryness under nitrogen stream. This fraction is named ether fraction. As a control, tar extract and ether fraction of tobacco were prepared in the same manner as above.

For the isolation of pyrolysis products, a preparative liquid chromatography was performed. Each 0.5 mL of ether fraction in 5 mL of acetonitrile was applied onto a WAKO packed column NQ2 (spherical silica, 30 to 50 μm, 30-cm by 24-mm ID) equipped with an ultraviolet (UV) (245-nm) monitor. The mobile phase was acetonitrile-concentrated ammonium hydroxide(500:1) and the flow rate was 5 mL/min. The fractions obtained by the column chromatography were rechromatographed until each product was pure.

Reaction and Synthesis of Pyrolysis Products

Reduction of Pyro-5—A solution of a few milligrams of pyro-5 in 1 mL of ether containing 30 mg of aluminum lithium hydride (LiAlH4) stood overnight. The reaction mixture was treated in the usual manner. The product was identical with dimethylamphetamine in all aspects.

Reduction of Pyro-7 and Pyro-8 with LiAlH4—Solutions of a few milligrams of pyro-7 and pyro-8 in 1 mL of ether containing 30 mg of LiA1H4 stood overnight. The CI-MS of product from pyro-7 showed MH^+ at m/z 178. The CI-MS of product from pyro-8 showed MH^+ at m/z 192.

Phenylacetone—Phenylacetone was synthesized from benzaldehyde and nitroethane by the Heinzelman method [3].

N-*Formylmethamphetamine*—By the Mehlenbacher method [4], acetic-formic anhydride was prepared by cooling two volumes of acetic anhydride to 0°C, slowly adding one volume of 99% formic acid, and heating at 50°C for 30 min. One hundred milligrams of methamphetamine HCl were dissolved in a solution of 1.5 mL of acetic-formic anhydride and heated at 50°C for 3 h. After cooling, the reaction mixture was added with 3 mL of water and extracted with 5 mL of ether three times. The ether layer was washed with 1% ammonium hydroxide and evaporated to give a pale yellow oil, which was chromatographed on silica gel eluating with chloroform to give 85 mg of the title compound. CI-MS (m/z): 178(MH^+, 100%), 86(30%). EI-MS (m/z): 86(M^+-91, 100%). IR(KBr): 1660 cm^{-1}(amido). PMR($CDCl_3$; δ ppm): 7.90 and 7.74 (double singlet, cis, and trans of NCHO).

Dimethylamphetamine—Dimethylamphetamine was synthesized from methylephedrine by the Rosenmund method [5]. It was crystallized as HCl salt, mp 157 to 158°C. CI-MS (m/z): 164(MH^+, 100%), 72(70%). EI-MS (m/z): 72(M^+-91, 100%). PMR($CDCl_3$; δ ppm): 2.64 [singlet,6H,$N(CH_3)_2$].

N-*Acetylmethamphetamine*—A solution of 100 mg of methamphetamine HCl in 1 mL of acetic anhydride and 0.5 mL of pyridine was heated at 80°C for 3 h. The reaction mixture

was treated in the usual manner to give 91 mg of pale yellow oil. CI-MS (m/z): 192(MH^+, 100%). EI-MS (m/z): 100(M^+-91, 30%), 58[(M^+-91)-$COCH_2$, 100%]. IR(KBr): 1640 cm^{-1} (amido). PMR($CDCl_3$; δ ppm): 1.70 and 1.92 (double singlet, cis, and trans of $COCH_3$).

N-*Propionylmethamphetamine*—A solution of 100 mg of methamphetamine hydrochloride in 1 mL of propionic anhydride and 0.5 mL of pyridine was heated at 80°C for 3 h. The reaction mixture was treated in the usual manner to give 102 mg of pale yellow oil. CI-MS (m/z): 206(MH^+, 31%), 114(M^+-91, 100%). EI-MS (m/z): 114(M^+-91, 18%), 58(100%). IR (KBr): 1630 cm^{-1} (amido). PMR($CDCl_3$; δ ppm): 0.95 and 1.04 (double triplet, cis, and trans of $COCH_2CH_3$), 1.90 and 2.12 (double quartet, cis, and trans of $COCH_2CH_3$).

N-*Cyanomethylmethamphetamine*—To a solution of 110 mg of methamphetamine HCl in 30 mL of dioxane was added 330 mg of sodium hydride (NaH) (60% containing mineral oil). Then 1.5 mL of bromoacetonitrile was added into the reaction mixture and kept standing for 20 h. After filtration, the solvent was evaporated to dryness. To the residue was added 1 mL of concentrated ammonium hydroxide and extracted with 3 mL of hexane three times. The combined hexane solution was evaporated under nitrogen stream. The residue was purified with silica gel chromatography eluating with chloroform to give 95 mg of pale yellow oil. CI-MS (m/z): 189(MH^+, 9%), 162(M^+ -CN, 100%). EI-MS (m/z): 97(M^+-91, 100%). IR (KBr): 2220 cm^{-1}(cyano). PMR ($CDCl_3$; δ ppm): 3.58 (singlet,NCH_2CN).

Results and Discussion

Most of Japanese methamphetamine abusers self-administer it by injections. However, abuse by smoking methamphetamine mixed in a cigarette has become somewhat epidemic in Japan because a dirty injection brings the dangers of AIDS [*6*] or other diseases and it leaves injection marks on skin. It is very interesting how much methamphetamine in a cigarette transfers into tar by smoking.

The results of experiments of smoking cigarettes mixed with a solution of methamphetamine HCl in methanol are shown in Fig. 2. In any case, recoveries of methamphetamine

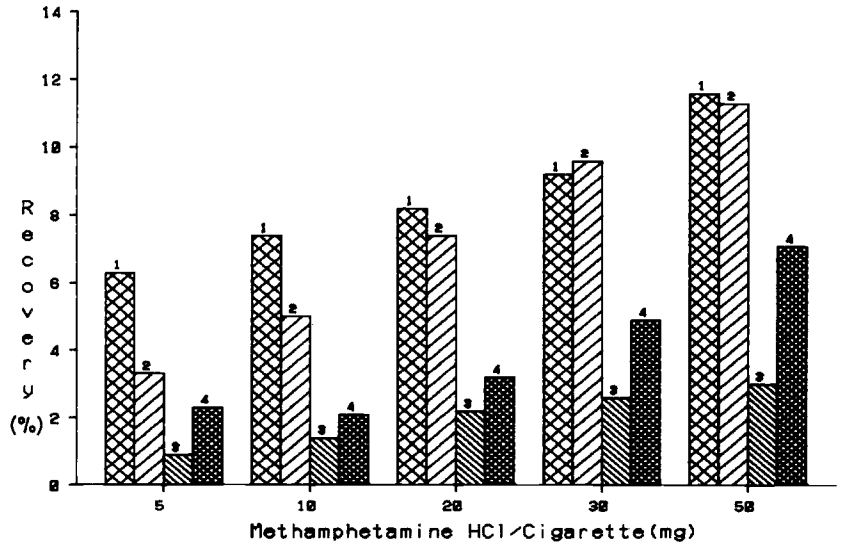


FIG. 2—*Effects of the amount of methamphetamine HCl added into nonfilter and filter cigarettes on its inhalation efficiency (nonfilter cigarette; tar:* 1, *butt:* 3, *filter cigarette; tar:* 2, *butt:* 4*).*

increased according to the increase of it in a cigarette. In the addition of 50 mg of methamphetamine, the inhalation efficiency of it becomes maximum and about 12% of this addition was transferred into tar. There were not big differences between the results of a nonfilter cigarette and a filter cigarette. However, in the addition of less than 10 mg of methamphetamine, the inhalation efficiency of it into tar in case of a filter cigarette was considerably less than that of a nonfilter cigarette. In the addition of more than 20 mg of methamphetamine, there were no differences of the inhalation efficiency into tar between both cigarettes. In all cases, methamphetamine which remained in butts of filter cigarettes was more than that of nonfilter cigarettes.

Inhalation efficiencies of methamphetamine into tar on various suction conditions were examined (Table 1). Inhalation efficiencies of it increased under conditions of shorter intervals and more suction volume than a standard method (60 s and 35 mL). The inhalation efficiency of methamphetamine into tar between HCl salt and free base was also examined (Table 2). In any case, there were no significant differences among the inhalation efficiencies of any form. Curiously enough, smoking free base methamphetamine in a cigarette did not give a higher inhalation efficiency of it into tar than that of HCl salt, unlike smoking cocaine free base, so-called "crack." The reason is not known yet, but it is presumed that methamphetamine's HCl salt in a cigarette becomes free base easily during smoking because tobacco contains a large amount of basic components [*7,8*].

Pyrolysis Products

Comparing GC/MS of tar from a cigarette containing methamphetamine and a control cigarette, it was clear that most of the higher boiling components were produced only by

TABLE 1—*Inhalation efficiency of methamphetamine into tar by various suction conditions.*

Suction Condition		Methamphetamine Added			
		10 mg		20 mg	
Volume, mL	Interval, s	Recovery, %[a]	Puff Times	Recovery, %	Puff Times
35	60	7.4 ± 0.5	10	8.2 ± 0.3	10-11
35	30	9.7 ± 0.7	14	14.1 ± 0.9	14-15
80	60	14.0 ± 1.0	7	17.3 ± 0.5	8

[a]Mean ± SD (n = 3).

TABLE 2—*Inhalation efficiency of methamphetamine into tar on the difference between HCl salt and free base (suction volume = 35 mL, interval = 60 s).*

State of Methamphetamine	Methamphetamine Added			
	10 mg		20 mg	
	Recovery, %[a]	Puff	Recovery, %	Puff
HCl salt				
Solution	7.4 ± 0.5	10	8.2 ± 0.3	10-11
Crystal	7.2 ± 0.6	10	7.4 ± 0.5	10
Free base	6.5 ± 0.3	10	9.2 ± 0.2	10-11

[a]Mean ± SD (n = 3).

smoking tobacco. GC/MS of the ether fraction is shown in Fig. 3. Pyrolysis products of methamphetamine were temporarily named pyro-1,-2,-3,-4,-5,-6,-7, and -8 according to the order from the earlier retention time. MS, IR, and PMR data of pyrolysis products are shown in Tables 3 and 4. By library research of standard MS spectral data [*9*] and the comparison between spectral data of pyrolysis products and synthetic or authentic samples, pyro-1 was identified as phenylacetone and pyro-2 was identified as amphetamine. Because pyro-3,-4,-5,-6,-7, and -8 resisted acetylation with trifluoroacetic anhydride, they were presumed to be tertiary amines or amides. Pyro-3 was inactive against the reduction with LiAlH4. CI-MS of pyro-3 showed MH^+ at m/z 164 and EI-MS of it showed M^+-91 at m/z 72, which shifted to $^+14$ from MH^+ and M^+-91 of methamphetamine, respectively. Pyro-3 was identical in all aspects with dimethylamphetamine synthesized from methylephedrine by the catalytic reduction [*5*]. Pyro-5, -7, and -8 were inactive with the reduction with NaBH4, but they were reduced with LiAlH4 to give the compounds of which MH^+ and the base peak of EI-MS are 14 smaller than that of the parent compounds. The reductive product of pyro-5 with LiAlH4 was identical with dimethylamphetamine. IR of pyro-5 showed the existence of a carbonyl group in its molecule at 1660 cm^{-1}. Because MH^+ of pyro-5 is 28 larger than MH^+ of methamphetamine, it was presumed to be *N*-formylmethamphetamine. PMR of pyro-5 showed the formyl protons of its cis- and trans-conformer at 7.90 and 7.74 ppm, respectively, as Barron et al. [*10*] have reported about the existence of the cis- and trans-conformer of *N*-acylamphetamines by PMR spectral analysis. Pyro-5 was identical with *N*-

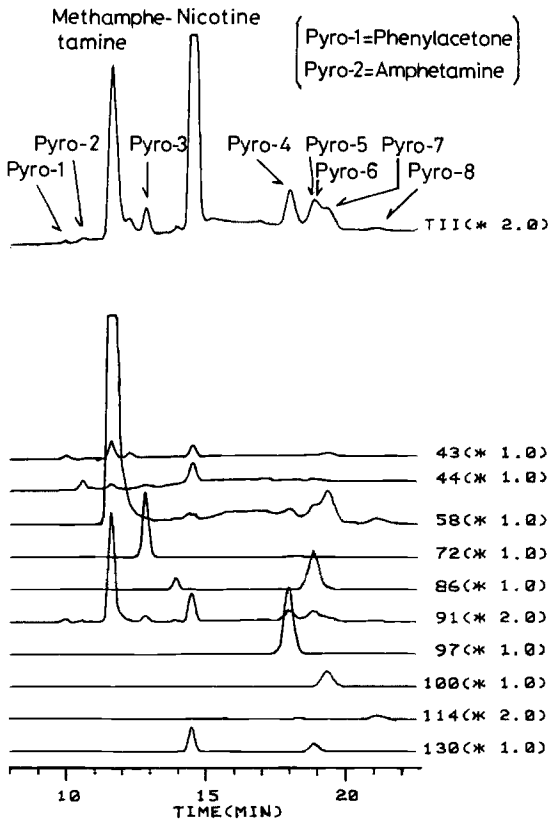


FIG. 3—*Mass chromatograms of ether fraction of the tar.*

TABLE 3—*The characteristic mass spectral and infrared spectral data of pyrolysis products.*

Products	CI-MS MH^+, %[a]	Base Peak	EI-MS M^+-91, %[b]	IR Spectra, cm^{-1}
MA[c]	150 (100)	...	58 (100)	...
Pyro-3	164 (100)	...	72 (100)	...
Pyro-4	189 (9)	162	97 (100)	2220 (cyano)
Pyro-5	178 (100)	...	86 (100)	1660 (amide)
Pyro-6	222 (97)	130	130 (100)	...
Pyro-7	192 (100)	...	100 (30)[d]	1640 (amide)
Pyro-8	206 (31)	114	114 (18)[d]	1630 (amide)

[a]Relative intensity to 100% peak over m/z 100.
[b]Relative intensity to 100% peak.
[c]Methamphetamine.
[d]Base peak = m/z 58.

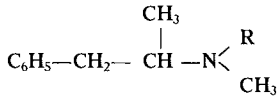
formylmethamphetamine synthesized by the formylation of methamphetamine. IR of pyro-7 and -8 showed the existence of a carbonyl group in their molecule at 1640 and 1630 cm^{-1}. MH^+ of pyro-7 is 42 larger and MH^+ of pyro-8 is 56 larger than MH^+ of methamphetamine, so pyro-7 and -8 were presumed to be *N*-acetylmethamphetamine and *N*-propionylmethamphetamine, respectively. They were identical with the synthetic *N*-acetyl- and *N*-propionylmethamphetamine in all aspects. IR of pyro-4 showed no carbonyl band and a cyano band at 2220 cm^{-1}. MH^+ of pyro-4 is 39 larger than MH^+ of methamphetamine. Reduction of pyro-4 with sodium borohydride (NaBH4) gave dimethylamphetamine. PMR of pryo-4 showed the existence of phenylpropyl portion at 7.1 to 7.3 ppm (phenyl protons); 1.03 ppm ($C—CH_3$), 2 to 3 ppm ($ArCH_2—$), and *N*-methyl at 2.48 ppm; and moreover a singlet peak for 2H at 3.58 ppm which was presumed to be $N—CH_2—CN$, as shown in Fig. 4. Cyanomethylation of methamphetamine with $BrCH_2CN$ and NaH gave a compound which is identical with pyro-4. Pyro-6 has not been identified yet.

A systematic diagram of pyrolysis of methamphetamine by smoking with tobacco is shown in Fig. 5. Smoking of methamphetamine mixed in tobacco gave various pyrolysis products by oxidation, demethylation, methylation, formylation, acetylation, propionylation, cyanomethylation, and so on. These facts raise various questions, for example, how different effects from that of injective abuse are produced by smoking abuse of methamphetamine or what kinds of pharmacological and toxicological effects each pyrolysis product has. Cyanomethylmethamphetamine of the largest pyrolysis product has a similar structure to 2-cyanoethylamphetamine that is fenproporex of an anorectic. It has been reported [*11,12*] that fenproporex was rapidly and extensively metabolized to amphetamine by dealkylation in body. Therefore, it is surely presumed cyanomethylmethamphetamine must be rapidly converted to methamphetamine in body. The inhalation efficiency of methamphetamine itself into tar by smoking was not high (<20%) no matter how changed the smoking manner was. However, formyl-, acetyl-, propionyl-, and cyanomethylmethamphetamine could easily be transferred into methamphetamine in the body, so the total active compounds in tar would considerably be larger.

Conclusion

In conclusion, methamphetamine itself transferred into tar by smoking was not large, 17% of an additive amount at most. Abuse of methamphetamine by smoking might be inefficient as an administered method of methamphetamine abuse. However, most pyrolysis

TABLE 4—*The assignment of PMR spectral data (δ ppm) of pyrolysis products.*



Products	N-R	NCH_2CN	NCHO cis/trans[a]	$NCOCH_3$ cis/trans	$NCOCH_2CH_3$ cis/trans	$CHCH_3$ cis/trans	NCH_3 cis/trans
Pyro-3	methyl	...	...	...	...	1.16 (CH_3)	2.64 (6H)
Pyro-4	cyanomethyl	3.58	...	...	...	1.03 (CH_3)	2.48
Pyro-5	formyl	...	7.90/7.74	...	...	1.12/1.25 (CH_3) 4.75/3.76 (CH)	2.77
Pyro-7	acetyl	...	...	1.92/1.70	...	1.07/1.21 (CH_3) 5.01/4.01 (CH)	2.73/2.79
Pyro-8	propionyl	...	...	...	1.04/0.95 (CH_3) 2.12/1.90 (CH_2)	1.10/1.24 (CH_3) 5.05/4.07 (CH)	2.77/2.87

[a]Conformers of cis and trans were assigned according to the report of Barron's group [8].

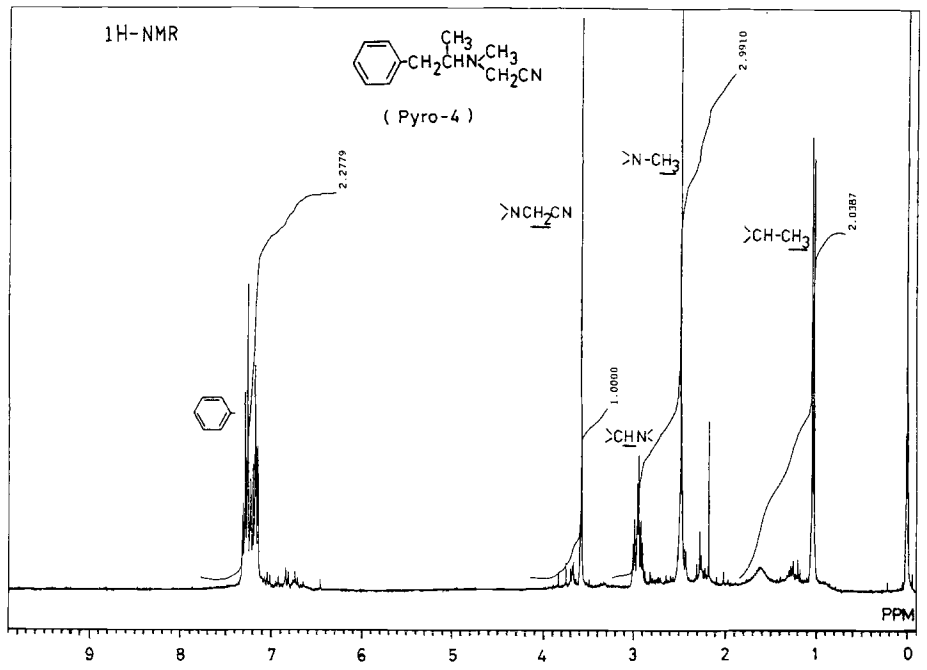


FIG. 4—*PMR spectrum of pyro-4 (cyanomethylmethamphetamine).*

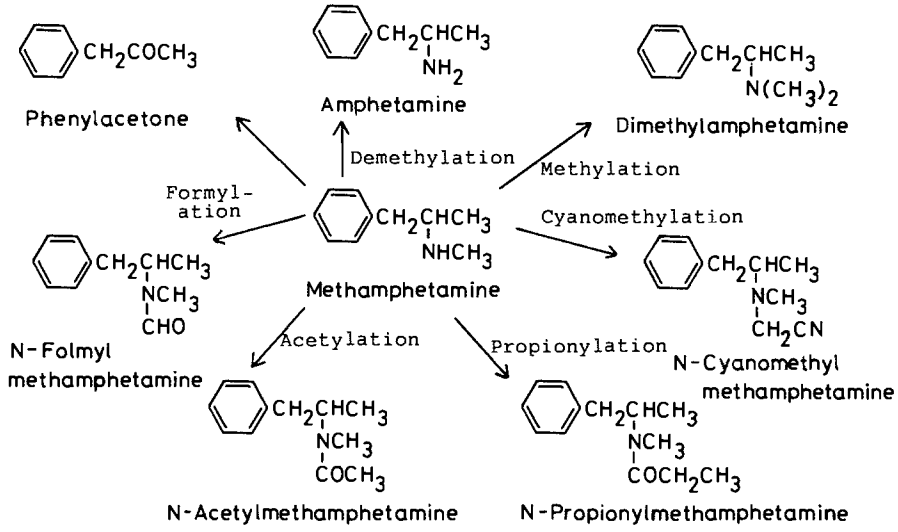


FIG. 5—*Pyrolysis patterns of methamphetamine in a cigarette by smoking.*

products identified in this study, such as dimethylamphetamine,*N*-formyl-,*N*-acetyl-,*N*-propionyl-, and *N*-cyanomethyl-methamphetamine, could easily be metabolized to methamphetamine in body. Though the amount of total active methamphetamine-like compounds in tar has not been determined yet, the inhalation efficiency by smoking of compounds which can be converted to methamphetamine in the body would not be low.

N-cyanomethylmethamphetamine, which is a new compound and the largest pyrolysis compound produced by smoking methamphetamine with tobacco, has been identified by IR,MS, and PMR data and comparison with the sample synthesized by BrCH2CN and methamphetamine with sodium hydride. It is very interesting that cyanomethylation of methamphetamine has occurred by smoking it with tobacco. The pharmacological and toxicological implications of *N*-cyanomethylmethamphetamine remain to be examined.

Acknowledgment

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