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Pyrolytic Fate of Piperidinocyclohexanecarbonitrile, A Contaminant of Phencyclidine, During Smoking

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Abstract

The pyrolysis products of 1-(1-piperidino)cyclohexanecarbonitrile (PCC), the major contaminant of illicit phencyclidine (PCP), have not been previously reported. In order to quantify PCC in mainstream smoke as well as to identify the pyrolysis products, [^{3}H]piperidino-[^{14}C]cyano-PCC was synthesized. Marijuana placebo cigarettes were impregnated with this double-labeled PCC and burned with an apparatus that simulated smoking. The mainstream smoke was passed through a series of traps containing glass wool, H_2SO_4, or NaOH. Approximately 75% of the ^{3}H was collected in these traps, and 46, 11, and 5% of the ^{14}C was found in the glass wool, H_2SO_4, and NaOH traps, respectively. Contents of the traps were analyzed by GC/MS. The glass wool trap contained 1-(1-piperidino)-1-cyclohexene, PCC, piperidine, and *N*-acetylpiperidine, and cyanide ion was detected in all three traps. Approximately 47% of the PCC was found intact in mainstream smoke. Approximately 58% was cleaved to form cyanide and 1-(1-piperidino)-1-cyclohexene. The latter was further broken down to cyclohexanone (which represented 21% of the starting material), piperidine (29%), and *N*-acetylpiperidine (7%), and about 2% remained intact.

Introduction

1-(1-Piperidino)cyclohexanecarbonitrile (PCC) is a major contaminant of phencyclidine (PCP). The most common illicit synthesis of PCP employs PCC as an intermediate which is not always removed from the final product (1–13). Exposure to PCC represents a potential health risk because PCC is considerably more toxic than PCP (5,8,9,12,14). Smoking PCP-impregnated cigarettes is a popular method of PCP abuse (15–18), which has prompted many investigators to study the pyrolysis and the delivery of PCP during smoking. At high temperatures, PCP is converted to numerous pyrolytic products (19), but only 1-(1-phenyl)-1-cyclohexene, piperidine, and *N*-acetylpiperidine have been found in cigarette smoke (20–24). PCC is readily degraded to 1-(1-piperidino)-1-cyclohexene, piperidine, and cyclohexanone during GC or TLC analysis or after prolonged periods in solution (4,5,8,11,14). The stability of PCC during smoking, however, has not been investigated despite the potential contribution its pyrolysis products may make to the pharmacology and toxicology of illicit PCP. The present study was conducted to determine the quantity of PCC in mainstream smoke and to identify and quantify pyrolysis products.

Materials and Methods

Chemicals and reagents

The K^{14}CN and [^{3}H]piperidine were obtained from New England Nuclear, and piperidine, cyclohexanone, KCN, and $NaHSO_3$ were purchased from Aldrich Chemical Co. Budget Solve was purchased from Research Products International Corp. Marijuana placebo cigarettes were kindly supplied by the National Institute on Drug Abuse. Acetylpiperidine was synthesized as previously described (24).

Synthesis of PCC and double-labeled PCC

PCC was synthesized according to previously described methods (1,2) with slight modifications. Two recrystallizations from methanol yielded PCC with an mp of 67–68°C. For the preparation of [^{3}H]piperidino-[^{14}C]cyano-PCC, cyclohexanone (294 mg, 3 mmol) was added to 2.5 mL of an aqueous solution of $NaHSO_3$ (343 mg, 3.3 mmol). This solution was cooled, 2 mL of an aqueous solution containing K^{14}CN (150 μCi/3.3 mmol, 213 mg) and [^{3}H]piperidine (120 μCi/3 mmol, 258 mg) was added, and this reaction mixture was stirred overnight at 0°C. The solution was filtered, and the product was washed twice with ice-cold water and dried in vacuo. The crude product was recrystallized twice from cold methanol to yield a product that was determined to be pure by GC/MS as described below. The specific activity of this product was determined to be 37 μCi of ^{3}H and 47 μCi of ^{14}C per mmol.

Synthesis of 1-(1-piperidino)-1-cyclohexene

The synthesis of 1-(1-piperidino)-1-cyclohexene was similar to that described by Godefroi et al. (3). Piperidine (1.70 g) and cyclohexanone (1.96 g) were added to benzene (12 g) and then distilled until all water and benzene were removed. The distillation was continued under reduced pressure (8 mm Hg) and the fraction at 105°C was collected as 1-(1-piperidino)-1-cyclohexene.

Pyrolysis studies

Marijuana placebo cigarettes (Δ^9-tetrahydrocannabinol was removed by ethanol extraction) were impregnated with one of the following solutions: double-labeled PCC (1 μCi of ^{3}H and 1.33 μCi of ^{14}C/20 mg of PCC/200 μL methanol), [^{3}H]-piperidine (2.1 μCi/15 mg/50 μL methanol), K^{14}CN (1 μCi/10 mg/200 μL of 80% ethanol), 1-(1-piperidino)-1-cyclohexene (40 mg/100 μL methanol), and cyclohexanone (2 mg/50 μL methanol). These cigarettes were smoked with the apparatus depicted earlier (24). Smoke was drawn by negative pressure through the following series of traps: 0.5 g of glass wool in a piece of tygon tubing (10 cm), an empty trap, 10 mL of 1N H_2SO_4, and 10 mL of 1N NaOH. Puffing was simulated by opening and closing the system to the vacuum for 7- and 4-s intervals, respectively. The flow rate was approximately 45 mL/7 s when the system was opened. Upon completion of smoking, the apparatus was disassembled for recovery of radioactivity. The glass wool traps were washed twice by forcing methanol (2 × 10 mL) through the tygon tubing. The glass wool was washed a third time by soaking in 10 mL of methanol after its removal from the tubing. The empty traps were also washed twice with 10-mL portions of methanol. Contents of the acid and base traps were removed and neutralized, and the containers were washed with 10 mL of methanol. The remainder of the cigarette (less than 0.5 cm) and the ash were transferred to a vial containing 10 mL of methanol (this solution is subsequently referred to as ash).

Instrumentation

Liquid scintillation spectrometry. Radioactivity was quantified by adding 50-μL aliquots of the samples to Budget Solve. The samples were placed in an LS 150 Scintillation Counter (Beckman Instruments, Inc.) for determination of radioactivity. External standardization was used to correct for quench. Quench curves were prepared with [^{3}H]water and [^{14}C]toluene, which allowed for compensation of interference between tritium and ^{14}C counting.

GC/MS. A Hewlett-Packard 5890A Gas Chromatograph-5970B Mass Selective Detector (GC/MS) was equipped with a fused-silica capillary column (0.2 mm × 12 m) coated with methyl silicone. The injection port was maintained at 185°C. A sample was injected, and after a 1-min purge, the initial oven temperature of 85°C was programmed to increase at a rate of 20°C/min until the final temperature of 210°C was reached. The flow rate of the carrier gas (He) was 0.74 mL/min. Other operating conditions were as follows: resolution of 800, accelerating voltage of 3.0 kV, electron energy of 70 eV, ion source temperature at 200°C, transfer line temperature at 275°C, and analyzer temperature at 180°C. Data were obtained with either the SCAN program, which allowed for repetitive acquisition of spectra, or the selected-ion mass (SIM) program, which enabled only preselected ions to be monitored for designated times. The computer system allowed the data from the SCAN program to be processed as a total-ion chromatogram or as a single-ion chromatogram (reconstructed chromatogram).

For identification of pyrolysis products, each standard (50 ng) was analyzed under the above conditions in order to obtain the mass spectra and the retention times. For quantitative analysis, standard concentration curves of PCC, piperidine, cyclohexanone, acetylpiperidine, and 1-(1-piperidino)-1-cyclohexene were obtained from SIM analysis of 5, 10, 50, and 100 ng of each compound just prior to sample analysis. The ions monitored for each standard are listed in Table II. The methanol extracts were injected into the GC/MS without any purification. It was necessary, however, to carry out an extraction of the aqueous samples before analysis. The contents of the acid and base traps were neutralized and shaken twice with 1-mL portions of hexane. These hexane extracts were then analyzed by GC/MS.

Determination of HCN

The method of Barakat et al. (25) was modified in order to quantify the small amounts of HCN produced from the pyrolysis of PCC. KCN (5, 10, 50, 100, and 200 μL of a 100mM solution) was mixed with 400 μL of a 100mM solution of Na_2HPO_4 (pH 8.4) and 2 μL of *N*-bromothymol blue in ethanol (0.4% w/v). The resulting solution was titrated with *N*-bromosuccinimide (1mM) until the indicator's blue color changed to a light yellow, and the volume was recorded. The pH of the samples in the acid and base traps was adjusted to 8.4, and 20-, 50-, and 100-μL aliquots were assayed immediately. Unfortunately, the yellow color of the methanol extract of the glass wool trap interfered with the HCN titration. Therefore, a 0.25-mL aliquot of the methanol extract was added to 9.75 mL of distilled water, which was in turn applied to a C_{18} SepPak column (Waters Associates). Prior to its use, the column was activated with 1 mL of methanol and rinsed with 5 mL of distilled water. The sample eluate was collected as fraction 1 (10 mL), and the column was subsequently washed with 1 mL of 10, 25, and 50% methanol/water (v/v) and finally with three 1-mL portions of 100% methanol which resulted in fractions 2–7. A 0.5-mL aliquot of each fraction was added to 10 mL of scintillation fluid for quantitation of radioactivity by liquid scintillation spectrometry. Aliquots (0.5 mL) of the SepPak fractions were also subjected to HCN analysis.

Results and Discussion

Pyrolysis of [^{3}H,^{14}C]PCC

The synthesis of [^{3}H,^{14}C]PCC provided a means of determining the recovery of radiolabeled PCC, as well as two of its moieties, from smoke. The smoke from four marijuana placebo cigarettes containing [^{3}H,^{14}C]PCC was collected as described above. The total recovery of radioactivity was 77 and 62% for tritium and ^{14}C, respectively (Table I). The major quantity of both radionuclides was contained in the glass wool trap; only 11 and 5% of the ^{14}C were in the acid and base traps, and less than 0.1% of the tritium was in the empty, acid, or base traps. The negligible quantities of radioactivity that remained in the

Table I. Recovery of Radioactivity from Cigarettes Impregnated with [^{3}H,^{14}C]PCC, [^{3}H]Piperidine, or K^{14}CN*

	[^{3}H,^{14}C]PCC		[^{3}H]Piperidine	K^{14}CN
Trap	Tritium	^{14}C	Tritium	^{14}C
Glass wool	75.2±18.9	45.6±0.3	39.2±8.5	31.1±3.6
Empty	ND	0.1±0.0	0.3±0.1	ND
Acid	ND	11.4±1.5	0.7±0.3	7.1±5.6
Base	ND	4.7±1.0	0.2±0.2	25.1±9.5
Ash	ND	0.2±0.1	0.1±0.1	0.5±0.2
Total	75	62	40	64

* Results are expressed as a percentage (mean ± SE, N = 4) of the radioactivity added to each cigarette. The following quantities were added: 1 μCi tritium/20 mg PPC; 1.33 μCi ^{14}C/20 mg PCC; 2.1 μCi tritium/15 mg piperidine; 1.0 μCi ^{14}C/10 mg KCN. ND = detectable.

ash demonstrated that all of the [^{3}H,^{14}C]PCC was either volatilized or pyrolyzed. The methanol was highly efficient in extracting the radioactivity from the glass wool (>98% removed with the first extraction). The GC/MS analysis of the first methanol extract of the glass wool filter is presented in Table II. Only 14% of the original [^{3}H,^{14}C]PCC was intact in this trap. The major portion appeared as 1-(1-piperidino)-1-cyclohexene, which is consistent with previous data showing that PCC is readily converted to this product under the high temperatures sometimes used for GC analysis (5,8,12,13,14,22). Cyclohexanone and piperidine, which were also present in appreciable quantities, could have arisen from either PCC or 1-(1-piperidino)-1-cyclohexene. While the formation of *N*-acetylpiperidine is not easily explained, the process is probably similar to the formation from PCP (24). The GC/MS analysis of the methanol extract of the glass wool trap did not reveal the presence of other pyrolysis products. Neither PCC nor any of the pyrolysis products mentioned above was detectable in the hexane extracts of the acid or base traps.

HCN was found in the glass wool, acid, and base traps. The colorimetric assay revealed that the acid and base traps contained 12.3 ± 1.2 and 4.9 ± 2.8 μmol (mean ± SD) of HCN, respectively, which represented 17.2% of the 100 μmol [^{3}H,^{14}C]PCC added originally. Analysis of the methanol extract of the glass wool trap was complicated by the presence of PCC, since the colorimetric assay did not distinguish PCC and HCN. Therefore, the methanol extract was subjected to C_{18} SepPak chromatography to separate these two substances and to eliminate the yellow color of the extract. The radioactivity that appeared in fractions 1–6 represented 2, 1, 2, 5, 57, and 15% of the ^{3}H added to the SepPak column, respectively. The percentages of ^{14}C added to the column that appeared in fractions 1–6 were 51, 4, 6, 14, 18, and 6, respectively. When [^{3}H]PCC was added to the SepPak column, radioactivity eluted in fractions 4–6. Moreover, the colorimetric assay showed that cyanide was present in fractions 1 and 2. These data taken collectively indicate that cyanide eluted in the first fractions while PCC was contained in fractions 4–6. The colorimetric analysis showed that the HCN in fractions 1 and 2 corresponded to 41% of the original 100 μmol of PCC. Therefore, the total HCN recovered in the glass wool, acid, and base traps represented 58% of the cyanide moiety in the starting material.

The above findings suggest that PCC is much less stable than PCP during smoking, since almost 60% of PCP was delivered intact in mainstream smoke (21,23). Interpretation of these data, however, is complicated by the fact that it was not possible to account for all of the radioactivity in the [^{3}H,^{14}C]PCC-impregnated cigarettes. In addition, it is possible that PCC, as well as 1-(1-piperidino)-1-cyclohexene, was unstable under the conditions required for isolation and sample analysis (1,5–7, 11,14). It is therefore likely that portions of the 1-(1-piperidino)-1-cyclohexene, piperidine, and cyclohexanone reported to be present in the glass wool trap were formed during the analysis. In order to address these issues, smoking experiments were conducted to determine recovery of the pyrolytic compounds and the degree to which they could be pyrolyzed.

Pyrolysis of 1-(1-piperidino)-1-cyclohexene

When cigarettes spiked with 1-(1-piperidino)-cyclohexene (40 mg) were smoked, GC/MS analysis of the methanol extract of the glass wool trap showed that very little of the 1-(1-piperidino)-1-cyclohexene was delivered intact (Table II). The major product was cyclohexanone, and lesser quantities of piperidine and *N*-acetylpiperidine were found. Also, 45% of the 1-(1-piperidino)-1-cyclohexene was broken down to piperidine and cyclohexanone during GC/MS under the conditions used for sample evaluation. Even when the degradation during GC/MS was taken into account, the quantity of 1-(1-piperidino)-1-cyclohexene in smoke would still be only 4.9% of that added originally.

Pyrolysis of [^{3}H]piperidine

The quantity of radioactivity was determined in all traps after the smoking of cigarettes containing 2.1 μCi/15 mg of [^{3}H]piperidine (Table I). The glass wool collected approximately 40% of the [^{3}H]piperidine, whereas the other traps contained only negligible quantities of radioactivity. GC/MS analysis of the glass wool extracts and the acid and base traps confirmed the results obtained with radioactivity. Interestingly, no *N*-acetylpiperidine was formed from [^{3}H]piperidine, although it was produced from both PCC and 1-(1-piperidino)-1-cyclohexene. These results suggest that a considerable proportion of the [^{3}H]piperidine is either lost in the sidestream smoke or not collected from the mainstream smoke.

Pyrolysis of cyclohexanone

Cigarettes containing cyclohexanone were smoked in the usual manner and gave almost complete recovery of cyclohexanone by the glass wool trap (Table II). GC/MS analysis of the methanol extract confirmed that the cyclohexanone remained intact during smoking and was efficiently trapped. Cyclohexanone was not detected in the other traps.

Pyrolysis of K^{14}CN

The recovery of radioactivity from cigarettes to which K^{14}CN had been added is presented in Table I. Approximately one third of the radioactivity was recovered in the acid and base traps.

Table II. GC/MS Analysis of Smoke Condensates (Glass Wool Traps) from Cigarettes Containing PCC, 1-(1-Piperidino)-1-cyclohexene, or Cyclohexanone*

Compound measured	t_R	Ions monitored		Recovery		
		Primary	Secondary	PCC	PCX	Cyclohexanone
Piperidine	1.6	84	57	11.6±3.1	8.4±2.3	—
Cyclohexanone	2.0	55	98	20.8±5.7	28.8±2.1	97.0±9.0
N-Acetylpiperidine	3.6	84	127	6.5±2.5	4.1±0.6	—
PCX	5.5	150	165	32.9±8.2	2.7±1.6	—
PCC	6.2	149	192	14.4±2.9	—	—

* The recovery of each compound is expressed as a percentage (mean±SD, N=4) of the material added: 0.1 mmol PCC, 0.24 mmol 1-(1-piperidino)-1-cyclohexene, or 0.02 mmol cyclohexanone. t_R = retention time; PCX = 1-(1-piperidino)-1-cyclohexene.

Conclusions

The recovery of PCC from the mainstream smoke of PCC-impregnated cigarettes was low as a result of its high volatility and low stability. Only 14% of the original [^{3}H,^{14}C]PCC was isolated from mainstream smoke, while 1-(1-piperidino)-1-cyclohexene, piperidine, *N*-acetylpiperidine cyclohexanone, and cyanide accounted for 33, 12, 7, and 40% of the original material as determined by GC/MS and colorimetric analysis. Because PCC can be converted to 1-(1-piperidino)-1-cyclohexene during GC/MS, the recovery of [^{3}H,^{14}C]PCC most likely represents a quantity less than that delivered. Additionally, the quantity of 1-(1-piperidino)-1-cyclohexene detected in PCC smoke most likely represents PCC that was delivered intact but was degraded during analysis, since the control experiments showed 1-(1-piperidino)-1-cyclohexene was completely degraded during pyrolysis. Therefore, the combined recoveries of PCC (14% of the original) and 1-(1-piperidino)-1-cyclohexene (33%) suggest that about 47% of the impregnated PCC was delivered intact during smoking. When the recovery of the pyrolytic products was taken into consideration, piperidine, *N*-acetylpiperidine, cyclohexanone, and hydrogen cyanide accounted for 29, 7, 21, and 58% of the original PCC. The ^{3}H was in the form of PCC, 1-(1-piperidino)-1-cyclohexene, piperidine, and *N*-acetylpiperidine, while PCC and HCN accounted for the ^{14}C. Additionally, *N*-acetylpiperidine was only detected in the pyrolyses of PCC and 1-(1-piperidino)-1-cyclohexene, but not in that of piperidine. Hence, the proposed route of PCC pyrolysis is initial degradation of PCC to 1-(1-piperidino)-1-cyclohexene and HCN followed by decomposition of 1-(1-piperidino)-1-cyclohexene to piperidine (8%), *N*-acetylpiperidine (4%), and cyclohexene (29%) (Figure 1).

The fatal dose of cyanide has been estimated to be in the range of 49 to 245 mg for an adult weighing 70 kg (26). Thienes and Haley (27) have reported the fatal dose to be as low as 33 mg, and Soine and Vincek (7) have reported that some illicit PCP contains up to 70% PCC. Smoking a PCP cigarette contaminated with PCC could therefore result in the delivery of a significant quantity of cyanide. It consequently poses pharmacological and toxicological risks to drug users.

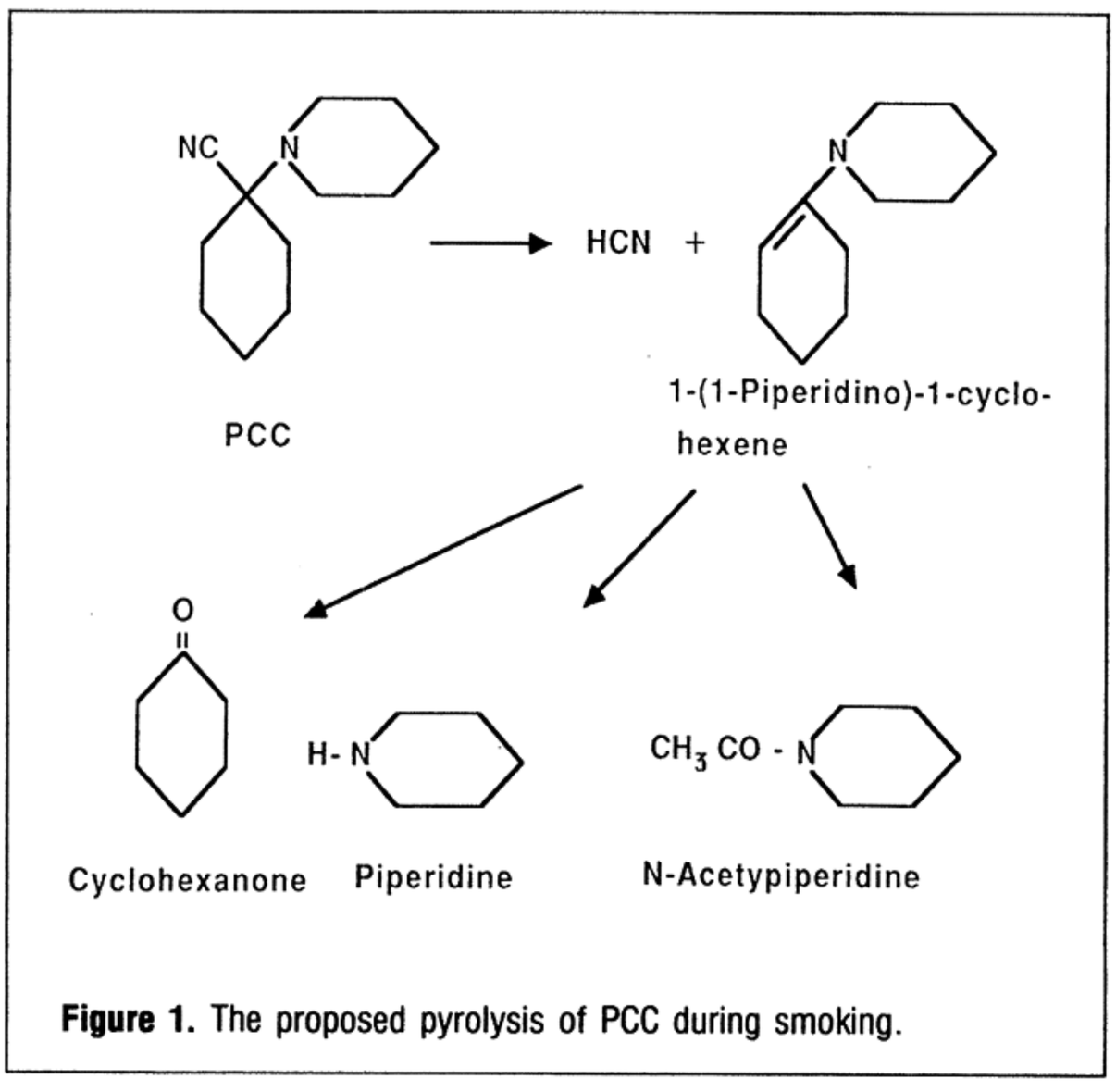

Figure 1. The proposed pyrolysis of PCC during smoking.

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