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Note

Separation and identification of phencyclidine precursors, metabolites and analogs by gas and thin-layer chromatography and chemical ionization mass spectrometry

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The illicit syntheses of new and potentially potent analogs of the psychotomimetic drug phencyclidine (PCP, "angel dust", "hog", "crystal") seem likely and indeed have begun. The thiophene analog TCP[1] and the N-ethyl analog PCE[2] have been positively identified in street samples.

Since our Center is engaged in the evaluation of the abuse potential of PCP analogs, a need arose for analytical methods suitable for product evaluation studies, identification of illicit samples, and for biological studies. Consequently, the chromatographic and mass spectral properties of a series of phencyclidine analogs and precursors were studied.

This note describes the application of thin-layer chromatographic (TLC) and gas–liquid chromatographic (GLC) methods for the separation and identification of the compounds shown in Table I. Additionally, their methane and isobutane chemical ionization (CI) spectra are reported. These techniques combine the simplicity and speed of TLC and GLC with the specificity of mass spectrometry (MS) to provide analytical methodology for the positive identification of these compounds.

EXPERIMENTAL

Instrumentation

For MS analysis, a Finnigan Model 3300 quadrupole gas chromatograph–mass spectrometer operating in the CI mode was employed. The GC–MS instrument was equipped with a Finnigan Model 6000 interactive data system. Methane (1000 μ pressure) and isobutane (500 μ pressure) were used as reagent gases. Electron voltage was maintained at 80 eV and the temperature of the source was 100°. Samples were analyzed via the solid probe inlet.

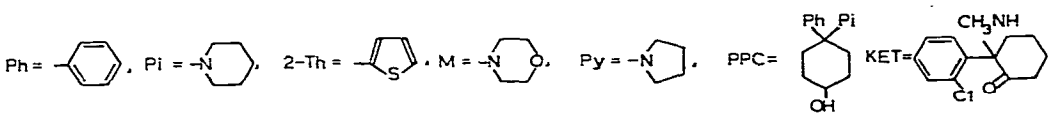
For GLC analysis, a Perkin-Elmer Sigma 2 or a Varian 2700 gas chromatograph was employed. They were equipped with a 1.8 m × 2 mm I.D. glass column packed with the liquid phase (3%) on Gas-Chrom Q (100–120 mesh). The injector and detector (flame-ionization type) were maintained at 160° and 250°, respectively. Nitrogen was used as the carrier gas at a flow-rate of 30 ml/min.

TABLE I

STRUCTURES OF PHENCYCLIDINE PRECURSORS, METABOLITES AND ANALOGS

Compound designation	R_1*	R_2*	*Name*
PCP	Ph	Pi	1-(1-Phenylcyclohexyl)piperidine
TCP	2-Th	Pi	1-[1-(2-Thienyl)cyclohexyl]piperidine
PPC*			4-Phenyl-4-piperidinocyclohexanol
PCHP	Ph	4-HO-Pi	1-(1-Phenylcyclohexyl)-4-hydroxypiperidine
PCC	CN	Pi	1-Piperidinocyclohexanecarbonitrile
PCM	Ph	M	1-(1-Phenylcyclohexyl)morpholine
TCM	2-Th	M	1-[1-(2-Thienyl)cyclohexyl]morpholine
MCC	CN	M	1-Morpholinocyclohexanecarbonitrile
PCPY	Ph	Py	1-(1-Phenylcyclohexyl)pyrrolidine
PYCC	CN	Py	1-Pyrrolidinocyclohexanecarbonitrile
PCDEA	Ph	$N(C_2H_5)_2$	N,N-Diethyl-1-phenylcyclohexylamine
DEACC	CN	$N(C_2H_5)_2$	1-Diethylaminocyclohexanecarbonitrile
PCE	Ph	NHC_2H_5	N-Ethyl-1-phenylcyclohexylamine
NMPCA	Ph	$NHCH_3$	N-Methyl-1-phenylcyclohexylamine
KET*			2-(*o*-Chlorophenyl)-2-(methylamino)-cyclohexanone

* Structural abbreviations are as follows:



TLC analysis was performed on silica gel (silica gel 60, E. Merck, Darmstadt, G.F.R.; Quanta Gram, Quantum, Fairfield, N.J., U.S.A.) and glass fiber sheets (ITLC-SA, Gelman, Ann Arbor, Mich., U.S.A.). The silica gel plates were heated for 1 h at 120° prior to use.

Standards and reagents

PCC, MCC, PYCC and DEACC were prepared by an adaptation of the procedure of Maddox *et al.*[3] for the synthesis of PCC. Their structural identity and purity were confirmed by TLC and MS. PCP and analogs were obtained from the Research Technology Branch, Division of Research, National Institute on Drug Abuse, Rockville, Md., U.S.A.

All other chemicals were of reagent grade quality.

RESULTS AND DISCUSSION

The chromatographic behavior of the analogs, precursors and metabolites of PCP on TLC and GLC is given in Tables II and III. CI mass spectra of methane and isobutane are tabulated in Table IV.

For TLC analysis, systems B and E (Table II) were superior to the other systems in separating PCP from the other compounds; however, none of the systems provided clean separations without some interference from other analogs. PCC has

TABLE II

R_F VALUES OF PHENCYCLIDINE PRECURSORS, METABOLITES AND ANALOGS

R_F values ($\times 100$) are reported as the mean of triplicate determinations. Plates were sprayed with potassium iodoplatinate for visualization of drug. *System A*: methylene chloride–*n*-butanol–aqueous ammonia (85:15:0.2), silica gel (Merck silica gel 60); *System B*: solvent system same as *system A*, silica gel (Quanta Gram); *system C*: ethyl acetate–methanol–aqueous ammonia–water (29:1:0.25:0.5), glass fiber plates impregnated with silicic acid (Gelman ITLC-SA); *system D*: ethyl acetate–methanol–dimethylamine (40% aqueous solution) (90:10:1.6), silica gel (Merck silica gel 60); *system E*: ethyl acetate–methanol–diethylamine (90:10:1.6), silica gel (Merck silica gel 60).

Compound	*TLC system*				
	A	*B*	*C*	*D*	*E*
PCP	27	58	94	70	72
TCP	54	75	90	85	84
PPC	—	16	39	57, 69**	26, 40**
PCHP	10	28	69	64	37
PCC*	0	—	0	92	92
PCM	88	95	95	93	89
TCM	91	97	95	90	93
MCC*	0	—	0	89	11
PCPY	11	23	71	40	26
PYCC*	0	—	0	0	2
PCDEA	36	57	95	89	79
DEACC*	92	100	94	86	—
PCE	25	45	80	60	43
NMPCA	17	24	56	60	22
KET	82	93	92	80	75

* Two spots are occasionally observed for these compounds owing to their instability on TLC
** Apparently a mixture of *cis* and *trans* isomers.

TABLE III

RELATIVE RETENTION DATA OF PHENCYCLIDINE ANALOGS AND METABOLITES

Values are the mean ($n = 3$) relative retention times. Values in parentheses represent uncorrected retention times in min.

Compound	*GLC column*			
	SE-30 (170°)	*OV-17 (180°)*	*OV-225 (180°)*	*Silar 5 CP (180°)*
PCP	1.00 (4.28)	1.00 (2.65)	1.00 (3.38)	1.00 (4.41)
TCP	0.17 (0.72)	1.02 (2.70)	0.22 (0.75)	0.26 (1.13)
PPC	2.31 (9.90)	3.28 (8.70)	6.35 (21.46)	2.94 (12.96)
PCHP	2.43 (10.40)	3.28 (8.70)	6.36 (21.50)	3.17 (14.00)
PCM	1.21 (5.20)	1.47 (3.90)	2.07 (7.00)	2.44 (10.76)
TCM	0.17 (0.72)	1.51 (4.00)	0.22 (0.75)	0.26 (1.13)
PCPY	0.74 (3.18)	0.79 (2.10)	0.77 (2.59)	0.78 (3.42)
PCDEA	0.16 (0.67)	0.42 (1.10)	0.37 (1.25)	0.35 (1.55)
PCE	0.29 (1.23)	0.28 (0.73)	0.30 (1.00)	0.31 (1.38)
NMPCA	0.28 (1.18)	0.29 (0.76)	0.31 (1.06)	0.34 (1.50)
KET	0.83 (3.57)	1.36 (3.60)	2.89 (9.76)	4.11 (18.13)

been reported to be unstable on TLC and GLC, easily eliminating a molecule of HCN to form an enamine[4]. This accounts for additional components seen inconsistently for PCC, MCC, PYCC and DEACC.

TABLE IV

CHEMICAL IONIZATION SPECTRA OF PHENCYCLIDINE ANALOGS AND METABOLITES

Compound	*Mol. wt.*	*Methane chemical ionization**				
		(M + 29)⁺	*(M + 1)⁺*	*M⁺*	*(M − 1)⁺*	*Prominent fragment ions***
PCP	243	272 (<1)	244 (26)	243 (65)	242 (33)	200 (13), 166 (10), 159 (40), 86 (100), 84 (43)
TCP	249	278 (2)	250 (24)	249 (54)	248 (19)	167 (11), 166 (65), 165 (100), 164 (11), 86 (37), 84 (37)
PPC	259	288 (0)	260 (27)	259 (41)	258 (27)	243 (19), 242 (91), 200 (28), 182 (13), 157 (52), 87 (19), 86 (100), 84 (26)
PCHP	259	288 (0)	260 (33)	259 (55)	258 (28)	242 (31), 216 (11), 182 (14), 159 (55), 102 (100), 100 (25), 84 (50)
PCC	192	221 (<1)	193 (14)	192 (20)	191 (42)	167 (47), 166 (100), 165 (20), 149 (11), 99 (10)
PCM	245	274 (1)	246 (14)	245 (41)	244 (18)	202 (10), 160 (14), 159 (100), 116 (11), 88 (83), 86 (25)
TCM	251	280 (2)	252 (6)	251 (13)	250 (4)	168 (15), 166 (13), 165 (100), 88 (10)
MCC	194	223 (4)	195 (26)	194 (8)	193 (14)	169 (25), 168 (100), 167 (13)
PCPY	229	258 (<1)	230 (40)	229 (100)	228 (57)	186 (25), 159 (66), 152 (17)
PYCC	178	207 (0)	179 (4)	178 (5)	177 (16)	153 (12), 152 (100), 99 (40)
PCDEA	231	260 (<1)	232 (35)	231 (100)	230 (39)	188 (18), 160 (13), 159 (93), 154 (14), 91 (16)
DEACC	180	209 (0)	181 (11)	180 (15)	179 (20)	165 (14), 155 (42), 154 (50), 108 (45), 100 (50), 99 (100), 98 (23), 81 (15)
PCE	203	232 (<1)	204 (25)	203 (47)	202 (35)	187 (11), 160 (47), 159 (100), 126 (20), 119 (11), 91 (16)
NMPCA	189	218 (<1)	190 (14)	189 (20)	188 (24)	160 (13), 159 (100), 146 (15), 119 (12), 112 (20), 91 (10)
KET***	237	266 (5)	238 (100)	237 (7)	236 (12)	220 (32), 209 (27), 207 (27), 180 (16), 179 (17), 125 (11)
	239	268 (2)	240 (34)	239 (17)	238 (100)	
		*Isobutane chemical ionization**				
		(M + 57)⁺	*(M + 1)⁺*	*M⁺*	*(M − 1)⁺*	*Prominent fragment ions***
PCP	243	300 (2)	244 (70)	243 (63)	242 (41)	245 (17), 200 (14), 159 (20), 86 (100), 84 (28)
TCP	249	306 (36)	250 (45)	249 (45)	248 (12)	307 (16), 251 (11), 166 (45), 165 (100), 164 (14), 86 (74), 84 (32)
PCC	192	249 (0)	193 (0)	192 (2)	191 (0)	166 (37), 165 (100)
PCM	245	302 (0)	246 (28)	245 (18)	244 (6)	160 (11), 159 (60), 88 (100)
TCM	251	308 (3)	252 (12)	251 (20)	250 (3)	168 (12), 167 (20), 166 (46), 165 (100), 164 (25), 88 (49)
MCC	194	251 (0)	195 (5)	194 (3)	193 (1)	168 (77), 100 (12), 99 (100), 84 (15)
PCPY	229	286 (2)	230 (100)	229 (82)	228 (50)	231 (20), 186 (25), 159 (30)
PYCC	178	235 (0)	179 (20)	178 (23)	177 (15)	153 (96), 152 (100), 151 (39), 135 (13), 110 (14), 99 (10)
PCDEA	231	288 (1)	232 (80)	231 (100)	230 (38)	188 (18), 160 (12), 159 (79)
PCE	203	260 (0)	204 (77)	203 (38)	202 (16)	201 (10), 160 (32), 159 (100)
KET***	237	294 (2)	238 (100)	237 (8)	236 (5)	241 (10), 209 (25)
	239	296 (1)	240 (59)	239 (39)	238 (100)	

* *m/e* (% abundance).

** Only ions ≥10% abundance are reported.

*** KET appears as two superposed spectra because of the isotopes of chlorine.

Using GLC, separation of PCP from analogs was possible on three of the four phases tested. Only OV-17 was not effective in separating PCP from the thienyl analog, TCP. Overall separation of all components was best on SE-30, the least polar phase used. Complete resolution of the metabolites PPC and PCHP was not achieved on any of the columns tested but partial resolution was achieved on SE-30.

CI-MS provided the most specific means of identification of PCP analogs, precursors, and metabolites. Generally, 1 μg of the sample introduced via the solid probe inlet gave well defined spectra sufficient for identification purposes.

As seen in Table IV, the mass spectra of these compounds resulting from methane-CI and isobutane-CI were quite similar in overall fragmentation patterns. Methane-CI generally produced a greater $M^+/(M+1)^+$ ratio than isobutane-CI. This was usually accompanied by a strong $(M-1)^+$ ion.

The $(M+29)^+$ and $(M+57)^+$ ions were weak and occasionally absent. Loss of a molecule of amine was quite evident in the spectra of the analogs and metabolites, whereas the major ion in the spectra of the precursors arose from the loss of HCN.

These systems were useful for product evaluation, stability studies and identification of illicit street samples. An example of the latter is the identification of PCE in a street sample obtained from local authorities. Initial inspection of the substance (pink powder) on TLC (systems A and B) revealed an iodoplatinate positive spot with R_F similar to that of PCE. GLC analysis on SE-30 revealed the presence of a component with retention time 1.26 min (retention time relative to PCP = 0.29).

Mass spectral analysis (methane-CI) provided the following spectrum: *m/e* (% abundance) 204 (15), 203 (38), 202 (24), 160 (35), 159 (100), 126 (20), 119 (12), 91 (23). Comparison of this spectrum with that of an authentic standard confirmed the identity of the illicit street sample as PCE.

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