Identification of a Nitrone as an *in vitro* Metabolite of *N*-Methylamphetamine†

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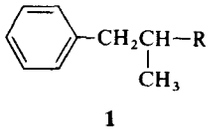
The relatively labile nitrone, α-methyl-(*N*-methylene)benzeneethanamine *N*-oxide was isolated from incubates of (±)-*N*-methylamphetamine with fortified liver homogenates from rats and rabbit. Identification of the nitrone was confirmed directly by gas chromatography and gas chromatography mass spectrometry and, after its conversion to isoxazolidine adducts by the action of methyl and ethyl acrylate. An authentic sample of the nitrone was synthesized unequivocally from *N*-hydroxyamphetamine and formaldehyde. The isomeric nitrone, *N*-(α-methylbenzeneethylidene)methylamine *N*-oxide, was also synthesized and its gas chromatographic and gas chromatographic mass spectrometric characteristics determined to confirm that the metabolically formed nitrone was not *N*-(α-methylbenzeneethylidene)methylamine *N*-oxide. Two previously unreported metabolites of (±)-*N*-methylamphetamine, *N*-hydroxyamphetamine and 1-hydroxy-1-phenyl-2-propanone, were isolated from rat *in vitro* experiments; the latter metabolite was not produced *in vitro* by rabbit liver homogenates.

INTRODUCTION

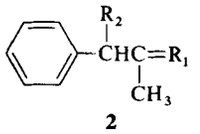
Previous studies[1] showed that *N*-methylamphetamine (NMA, **1a**) was metabolized by fortified rat liver homogenates to a number of products including 1-phenyl-2-propanone oxime (**2b**). The amount of oxime **2b** increased significantly when incubates were strongly basified prior to extraction, indicating that a chemically unstable precursor of **2b** was present in the incubation mixture. The precursor could not be detected by the GC system employed at that time, but evidence was presented[1] which tentatively identified it as *N*-[(1-methyl-2-phenyl)ethyl]methanimine *N*-oxide (**1c**).§ Further evidence was required to confirm the identification of the *N*-methylene nitrone **1c**.



1

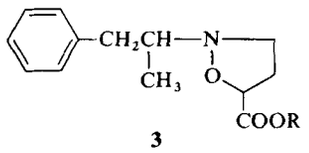
1a: R = –NHCH$_3$
1b: R = –N(OH)CH$_3$
1c: R = –$\overset{+}{N}$(O$^-$)=CH$_2$
1d: R = –NHOH
1e: R = –NH$_2$
1f: R = –NO$_2$
1g: R = –OH

† Abbreviation: NMA = *N*-methylamphetamine.
‡ Author to whom correspondence should be addressed.
§ Compounds possessing the structure $R^1R^2C{=}\overset{+}{N}(R^3){-}O^-$ have been named as derivatives of 'nitrone' ($CH_2{=}\overset{+}{N}H{-}O^-$),[2] as imine *N*-oxides[3] and as amine *N*-oxides.[4] The current Chemical Abstracts name for the nitrone **1c** is α-methyl-(*N*-methylene)benzeneethanamine *N*-oxide.



2

2a: R$_1$ = $\overset{+}{N}$(O$^-$)–CH$_3$; R$_2$ = H
2b: R$_1$ = N–OH; R$_2$ = H
2c: R$_1$ = O; R$_2$ = H
2d: R$_1$ = O; R$_2$ = OH



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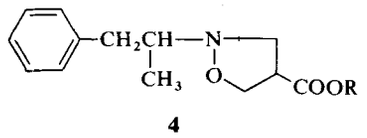
3a: R = CH$_3$
3b: R = CH$_2$CH$_3$



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4a: R = CH$_3$
4b: R = CH$_2$CH$_3$

EXPERIMENTAL

All materials were either available commercially, or were synthesized by standard procedures or as described below. The GC analyses were performed on a Perkin-Elmer gas chromatograph model 990 using helium as the carrier gas (60 ml min^{-1}); system A: 1% Carbowax 20M coated on Chromosorb W, 80/100 mesh, packed in a 1.1 m glass column of 4 mm i.d.; system B: 3.8% OV-101 coated on Chromosorb 750, 80/100 mesh packed in a 2.2 m glass column of 4 mm i.d. Retention times (t_r) are reported in minutes. Combined GCMS was performed on a Hewlett Packard HP5710A gas chromatograph coupled to a model HP5980A mass spectrometer employing similar GC columns to those described above. Helium was the carrier gas (60 ml min^{-1}), the ion source temperature was 190 °C, and the ionizing energy, 70 eV. Infrared

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spectra were run on a Perkin-Elmer 267 spectrophotometer as thin films or KBr discs, and NMR spectra were recorded on a Varian EM360A spectrometer as 10% solutions in $CDCl_3$ using tetramethylsilane as the internal standard. TLC was performed on silica gel GF_{254} plates (Merck, 0.25 mm thick) developed in ethyl acetate. Spots were visualized either by UV light (λ254 nm), or by spraying with Dragendorff's reagent (basic compounds gave a yellow/orange to red/orange color) or Tollen's reagent (reducing compounds gave intense black spots at room temperature).

Synthesis of *N*-hydroxyamphetamine (1d)

1-Phenyl-2-propanone oxime, *anti* isomer[5] (**2b**, 14 g, 93.8 mmol) was reduced with sodium cyanoborohydride (6.0 g, 95.5 mmol) in methanol (150 ml) at pH 3–4 by the method of Morgan and Beckett,[6] to yield 17.43 g (95% yield) of the neutral oxalate salt of the title compound, m.p. 171.5–172.5 °C (lit.[7] 175–176 °C).

Synthesis of *N*-hydroxy-*N*-methylamphetamine (1b)

Compound **1b** was synthesized by reductive hydroxyamination of 1-phenyl-2-propanone (3.0 g, 22.36 mmol) with methylhydroxylamine hydrochloride (1.84 g, 22.03 mmol) and sodium cyanoborohydride (1.5 g, 23.86 mmol) in methanol (50 ml) at pH 5–6 by the method described by Morgan and Beckett.[6] The oxalate salt of the title compound was prepared by the addition of oxalic acid in dry ether to an ether solution of the base **1b**: first fraction, m.p. 148–149 °C (1.7 g, 8.10 mmol) neutral oxalate; calc. for $C_{11}H_{16}NO_3$: C, 62.86; H, 7.62; N, 6.67%; found: C, 62.88; H, 7.80; N, 6.80%; NMR (10% in [$^2H_6$]DMSO) NO$\underline{H}$ and $\frac{1}{2}$(COO$\underline{H}$)$_2$ protons δ8.0, broad singlet. A second fraction was obtained m.p. 127–128 °C (0.55 g, 2.16 mmol) acid oxalate; calc. for $C_{12}H_{17}NO_5$; C, 56.47; H, 6.67; N, 5.49%; found: C, 55.70; H, 6.66; N, 5.55%; NMR (10% in [$^2H_6$]DMSO) NO$\underline{H}$ and (COO$\underline{H}$)$_2$ protons δ10.6, broad singlet; total yield 46% [lit.[8] m.p. of neutral salt (erroneously reported as the acid oxalate) 147–149 °C. A mixture of the neutral and acid oxalates of **1b** was apparently obtained in the earlier study[8] but not suspected. The reported m.p. and the elemental analyses were of different purified fractions.]

Synthesis of α-methyl-(*N*-methylene)benzeneethanamine *N*-oxide (1c)

To *N*-hydroxyamphetamine (**1d**, extracted from the neutral oxalate, 1.30 g, 6.63 mmol, by partition between potassium carbonate solution and ether) in benzene (150 ml) was added 37% formaldehyde solution (1.31 g, 16.13 mmol). The solution was refluxed in a Dean Stark apparatus until no more water was collected in the side arm (about 4 h). The benzene was evaporated *in vacuo* leaving a colorless oil. The last traces of benzene were removed by a stream of nitrogen and the oil was stored under nigrogen at −5 °C. An NMR spectrum was consistent with that expected from the title nitrone, and indicated the oil was at least 95% pure: δ1.52 (*d*, J = 6.5 Hz, 3, C$\underline{H}_3$) 2.85 and 3.28 (dq, J = 5.6 and 8.6 Hz, 2, CHC$\underline{H}_2$) 4.05 (m, 1, C$\underline{H}$) 6.00 and 6.32 (dd, J = 7.5 and 7.5 Hz, 2, N=C$\underline{H}_2$) 7.40 (s, 5, $\underline{Ar}$); IR (film) ν_{max} 700(s), 740 (m) 1065(s), 1275(m), 1300(m), 1450(m), 1490(m), 1560(s), 2920(m), 2970(m), 3020(m), cm^{-1}. MS (direct inlet) *m/e* (% relative abundance): 163([M]$^+$, 2), 148 (50), 118 (73), 117 (74), 115 (12), 104 (36), 91 (100), 77 (11), 65 (21), 56 (46), 51 (10), 42 (18). Calc. for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58%. Found: C, 73.36; H, 8.15; N, 8.33%.

Synthesis of methyl 2-(1-benzyl)ethylisoxazolidine-5-carboxylate (3a)

To α-methyl-(*N*-methylene)benzeneethanamine *N*-oxide (**1c**, 0.5 g, 3.07 mmol) was added stabilized methyl acrylate (0.5 g, 5.81 mmol), and an exothermic reaction ensued. TLC of the solution, 10 min after mixing the reagents, showed the nitrone (**1c**) was absent, but two new spots were present which gave an orange/red color when sprayed with Dragendorff's reagent (R_f 0.43 and 0.48 due to two diastereoisomers of the isoxazolidine adduct, **3a**). GCMS of the eluted spots gave identical results (see Table 1). Excess methyl acrylate was removed *in vacuo* to leave a straw colored oil which was a mixture of the diastereoisomers of **3a**: NMR ($CDCl_3$)δ1.00 (broad d, 3, CHC$\underline{H}_3$) 2.2–3.4 (m, 7, C$\underline{H}_2$C$\underline{H}_2$ and C$\underline{H}_2$C$\underline{H}$N) 3.79 (s, 3, OC$\underline{H}_3$) 4.59 (broad dd, 1, OC$\underline{H}$CH$_2$) 7.26 (s, 5, $\underline{Ar}$), IR (film) ν_{max} 700 (m), 750 (m), 1090 (m), 1175 (m), 1205 (m), 1450 (m), 1730 (s), 1750(s), 2800–3080 (m) cm^{-1}. See Table 1 for GCMS.

Synthesis of ethyl 2-(1-benzyl)ethylisoxazolidine-5-carboxylate (3b)

The ethyl acrylate adduct (**3b**) of the nitrone (**1c**) was obtained in the manner described above for **3a**, as a colorless oil which gave two orange spots on TLC after spraying with Dragendorff's reagent (R_f 0.46 and 0.52). Eluted (unsprayed) spots gave virtually superimposable GC mass spectra (see Table 1). The isoxazolidine (**3b**) formed an HCl salt, m.p. 93–96 °C. NMR (base) δ1.05 (broad d, 3, CHC$\underline{H}_3$) 1.30 (t, 3, CH$_2$C$\underline{H}_3$) 2.3–3.6 (m, 7, C$\underline{H}_2$C$\underline{H}_2$ and C$\underline{H}_2$C$\underline{H}$N) 4.27 (q, 2, C$\underline{H}_2$CH$_3$) 5.62 (dd. 1, OC$\underline{H}$CH$_2$) 7.28 (s, 5, $\underline{Ar}$); IR (HCl salt, KBr disc) ν_{max} 700 (m), 745 (m), 1020 (m), 1180–1230 (s, max. at 1195), 1745 (s), 2100–2650 (s, max. at 2440), 2800–3100 (m, max. at 2945) cm^{-1}. Calc. for $C_{15}H_{22}NO_3Cl$: C, 60.10; H, 7.01; N, 4.67%. Found: C, 59.65; H, 7.45; N, 4.52%.

Reaction of 1-phenyl-2-propanone with *N*-methylhydroxylamine

To methylhydroxylamine hydrochloride (6.3 g, 75.43 mmol) in water (10 ml) was added sufficient 1 M NaOH to obtain a solution of pH 8. 1-Phenyl-2-propanone (**2c**, 2.0 g, 14.93 mmol) was added in benzene (150 ml) and the mixture refluxed in a Dean Stark apparatus until no more water was collected (about

Table 1. TLC, GC and MS characteristics of *N*-methylamphetamine (1a) and its metabolites

Compound	TLC R_f	GC (system A)[b] t_r (min)	GCMS (system A) *m/e* (% relative abundance)[c]
1a	0.06[a]	0.73	149([M]‡, absent) 91(5) 65(5) 58(100)
1b	0.31[a]	9.9	164([M−1]⁺, 3) 148(6) 118(13) 117(16) 91(31) 74(100) 58(33) 56(28)
1c	0.10[a]	24.2	163([M]‡, 2) 148(51) 118(75) 117(79) 115(12) 104(39) 91(100) 77(10) 65(16) 56(30)
1d	0.33[a]	11.7	151([M]‡, absent) 119(4) 92(12) 91(46) 65(28) 60(100) 44(38) 42(15)
1e	0.07[a]	0.77	136([M+1]⁺, 4) 134([M−1]⁺, 6) 120(20) 117(12) 115(14) 103(10) 92(27) 91(76) 77(11) 65(27) 44(100)
1f	0.64	5.5	165 ([M]‡, absent) 117(19) 92(10) 91(100) 77(11) 65(20) 51(21) 41(29)
1g	0.54	2.0	136([M]‡, 2) 92(100) 91(70) 65(22) 45(28)
2a	0.02	36.0 (120 °C)	163([M]‡, 57), 146(67) 131(100) 130(31) 117(30) 115(29) 105(24) 91(33) 56(16)
2b	0.60	19.2	149([M]‡, 100) 132(28) 131(40) 130(33) 117(42) 116(69) 105(13) 92(23) 91(89) 90(20) 89(18) 65(14)
2c	0.64	1.25	134([M]‡, 83) 92(44) 91(100) 65(23) 43(26)
2d	0.54	7.1	150([M]‡, 8) 107(100) 105(65) 79(80) 77(65) 51(10) 43(6)
3a	0.43+0.48	40.9 (120 °C)	249([M]‡, absent) 190(2) 158(100) 98(8) 91(20)
3b	0.46+0.52	47.8 (120 °C)	263([M]‡, absent) 190(3) 173(11) 172(100) 144(19) 98(12) 91(20)

[a] These spots tail slightly.
[b] Oven temp. 100 °C unless stated.
[c] Diagnostic ions and ions of relative abundance > 10%

8 h). The organic layer was decanted and evaporated *in vacuo* to yield a pale brown oil. GC examination of the product showed one main component of t_r 36 min (system A, 120 °C) which comprised 73% of the total integrated areas of the peaks, and gave the following GCMS: *m/e* (% relative abundance) 163 ([M]‡, 57) 146 (67), 131 (100), 130 (30), 117 (30), 115 (29), 105 (24), 91 (33), 56 (16), consistent with the product being *N*-(α-methylbenzeneethylidene) methylamine *N*-oxide (**2a**).

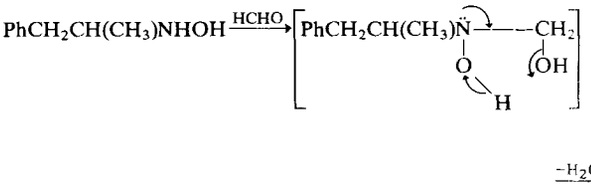
Metabolism experiments

Male Wistar rats (250–350 g) and a male New Zealand White rabbit (approx. 4 kg) were used. The livers were homogenized in 1.15% w/v KCl solution using a Potter homogenizer and the supernatants were prepared by centrifugation at 12 000 g (average). Erlenmeyer flasks (25 ml capacity) containing (±)-*N*-methylamphetamine hydrochloride (10 μmol), glucose-6-phosphate (20 μmol), $NADP^+$ (4.4 μmol), magnesium chloride (20 μmol) and liver homogenate 12 000 g supernatant (equivalent of 0.25 g liver) in 0.1 M phosphate buffer at pH 7.4 (total volume, 6 ml) were incubated at 37 °C for 60 min and extracted three times with freshly distilled diethyl ether. The combined ether extracts (15 ml) were evaporated in tapered evaporating tubes on a water bath (45 °C) until almost dry and then cooled in ice prior to analysis. Suitable blank incubations were performed by separately omitting cofactors or substrate or liver homogenate from the incubation mixture described above.

The extracts were subjected to GC (system A), GCMS (system A) and TLC analyses. Ethyl acrylate or methyl acrylate (*c.* 20 μl) was added to some extracts, mixed and the products subjected to similar analyses. The TLC spots were located (aided by UV light and Dragendorff's reagent sprayed on one edge of the plate), extracted with ether and subjected to GCMS analysis.

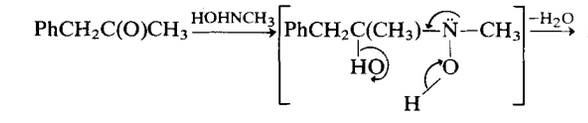
RESULTS AND DISCUSSION

The *N*-methylene nitrone (**1c**) was synthesized in excellent yield by the condensation of *N*-hydroxyamphetamine with formaldehyde (Scheme 1). The



Scheme 1

nitrone **1c** was chromatographed with no detectable decomposition using a different GC instrument and different columns to those employed previously.[8] The direct inlet and GC mass spectra of the nitrone **1c** were identical, but differed from the previously published[3] spectrum in that they lacked the ions *m/e* 146 and *m/e* 131. This observation raised doubts as to the purity of the nitrone synthesized previously by mild oxidation (yellow mercuric oxide) of *N*-hydroxy-*N*-methylamphetamine (**1b**). A possible explanation was that the nitrone synthesized previously was contaminated with small amounts of the isomeric nitrone (**2a**). Therefore, synthesis of this *N*-methylnitrone was attempted by the condensation of *N*-methylhydroxylamine with 1-phenyl-2-propanone (**2c**) (Scheme 2). The oily product gave one major spot on TLC and one major peak on GC; unidentified impurities were also present. GCMS of the major peak, t_r = 36 min (system A) had abundant

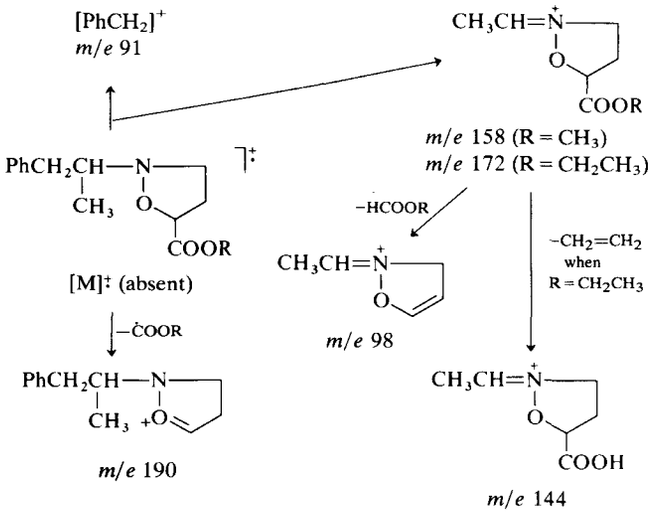


Scheme 2

ions at *m/e* 163 $[M]^{\ddagger}$, 146 $[M-OH]^{+}$ and *m/e* 131 $[M-OH-CH_3]^{\ddagger}$ (see Table 1). Purification of the product by column chromatography was attempted; however, decomposition occurred to give unidentified products. Attempts to isolate pure nitrone **2a** from the reaction mixture have been unsuccessful so far. The mild oxidation of *N*-hydroxy-*N*-methylamphetamine (**1b**) was repeated as described previously.[1] GC and NMR evidence indicated the product contained 90–95% of the *N*-methylene nitrone **1c** (t_r = 24.2 min system A), and a small amount of another product which had a GC retention time and mass spectrum identical to the synthesized nitrone **2a**. When the product was introduced into the mass spectrometer via the direct probe, ions attributable to **1c** were seen initially, but when most of the sample had volatilized, ions of *m/e* 131 and 146 appeared, derived from the less volatile isomer **2a**. Thus, mild oxidation of the secondary hydroxylamine with mercuric oxide gave an approximately 20 : 1 mixture of the isomeric nitrones **1c** and **2a** and the previously published[1] mass spectrum, identified as that of **1c**, was in fact the spectrum of a mixture of **1c** and **2a**.

Many nitrones, particularly of the type $R_1R_2CHN(O)CH_2$, are easily hydrolyzed[6] to formaldehyde and a primary hydroxylamine. We sought a method of stabilizing nitrones by preparing derivatives which could be used for identification purposes. Methyl acrylate and ethyl acrylate reacted quickly and quantitatively (NMR and TLC evidence) with the synthetic nitrone **1c** to form substituted isoxazolidines. Two isomeric adducts are possible from the reaction of methyl acrylate with the nitrone **1c**, namely methyl 2-(1-benzyl)ethylisoxazolidine-5-carboxylate (**3a**) and methyl 2-(1-benzyl)ethylisoxazolidine-4-carboxylate (**4a**). However, an NMR spectrum indicated that only the former isomer (**3a**) was present. A one proton overlapping doublet of doublets signal centered at δ4.59 was attributed to the 5-methine proton of structure **3a**. The alternative 2,4-disubstituted isoxazolidine (**4a**) would give an eight line signal (two doublets of doublets) due to coupling of its methine proton to the two adjacent, nonequivalent methylene groups. Since the ratio of the doublet of doublets integral (from **3a**) to the aromatic integral was 1 : 5, it is unlikely that more than 5% of the 2,4-isomer, if any, was present in the product. Significant broadening of the methine doublet of doublets signal and of the sidechain methyl group doublet signal is probably due to the product being a mixture of two diastereoisomers (two chiral centers are present). The product gave two spots on TLC which, when eluted separately and run on GCMS, gave GC peaks of similar retention times and virtually superimposable mass spectra which would be expected of diastereoisomers (see Table 1). Similar data were obtained from the product of reaction of the nitrone **1c** and ethyl acrylate. Therefore, this product is identified as a mixture of the diastereoisomers of ethyl 2-(1-benzyl)ethylisoxazolidine-5-carboxylate (**3b**). The mass spectra of the two isomers of **3b** (R_f 0.48 and 0.54) were also identical (Table 1). The mass spectra of **3a** and **3b** are interpreted readily (Scheme 3) and are much more diagnostic than the spectrum of the nitrone itself.

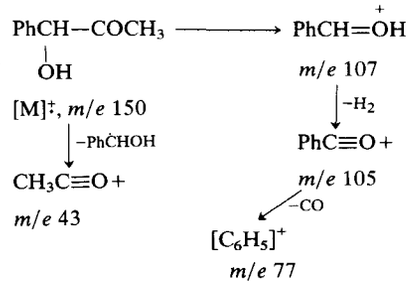
Having established methods to synthesize, derivatize and identify the nitrone **1c**, the *in vitro* metabolism of



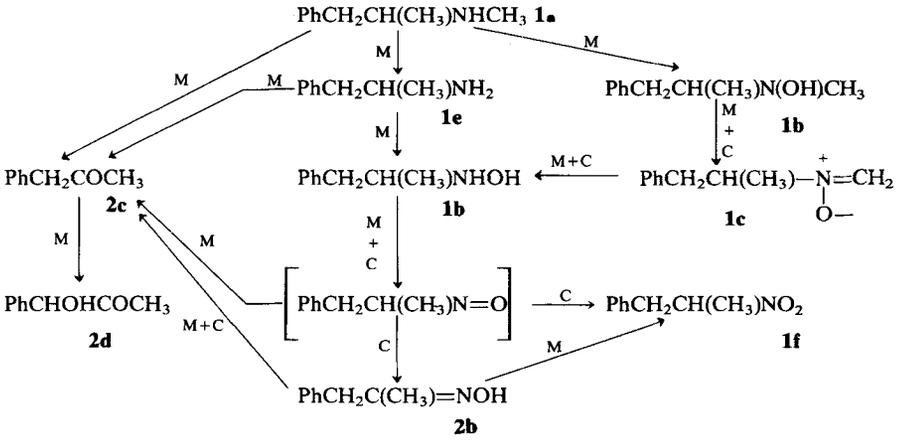
Scheme 3

NMA by fortified rat liver homogenates was repeated. The cofactor-dependent formation[1] of amphetamine (**1e**), 1-phenyl-2-propanone (**2c**), 2-nitro-1-phenylpropane (**1f**), *N*-hydroxy-NMA (**1b**) and 1-phenyl-2-propanone oxime (**2b**) was confirmed (for TLC and GCMS data, see Table 1). In addition, three other metabolic products were identified conclusively, the major one of which was deduced to be the nitrone **1c**, for the following reasons. The retention time of the metabolite on GC system A was identical to that of the synthetic nitrone **1c**, and gave an identical mass spectrum (GC inlet). The extracts were then treated separately with methyl acrylate or ethyl acrylate and examined by TLC. Plates sprayed with Dragendorff's reagent showed two orange/red spots with R_f values identical to those of the diastereoisomers of methyl 2-(1-benzyl)ethylisoxazolidine-5-carboxylate (**3a**) if methyl acrylate was used, or ethyl 2-(1-benzyl)ethylisoxazolidine-5-carboxylate (**3b**) when ethyl acrylate was employed to derivatize the nitrone. Both diastereoisomers of **3a** and of **3b** were separated adequately on TLC from other components in the extract that gave a color with Dragendorff's reagent. The identities of these isoxazolidine derivatives were confirmed by GCMS analysis of eluates of TLC spots (unsprayed).

The minor metabolite of NMA, GC t_r 11.7 min, was identified as *N*-hydroxyamphetamine (**1d**) when its mass spectrum (GC inlet) was examined. The base peak in the spectrum was of *m/e* 60; this fragment,



Scheme 4



Scheme 5. Proposed metabolic pathways for the *in vitro* metabolism of *N*-methylamphetamine in rats. M = metabolic reaction. C = chemical reaction [ ] not isolated

$[CH_3CH{=}NHOH]^+$, is a characteristic ion in the mass spectra of *N*-hydroxyamphetamine and its homologs.[9] Other abundant ions in the spectrum of the minor metabolite were identified readily: *m/e* 91, $[C_7H_7]^+$; *m/e* 65, $[C_5H_5]^+$; and *m/e* 44 $[CH_3CH{=}NH_2]^+$, and were consistent[9] with the structure **1d**. A synthetic sample of **1d** was prepared; it has a GC retention time and a mass spectrum identical to those of the metabolic product. Both the synthetic and metabolically produced compounds reduced ammoniacal silver nitrate solution rapidly as expected of an hydroxylamine structure.

The other minor metabolite of NMA, GC t_r 7.1 min, gave a mass spectrum (see Table 1) which was consistent (Scheme 4) with the metabolite being 1-hydroxy-1-phenyl-2-propanone (**2d**). A synthetic sample of **2d** has comparable GC and GCMS properties.[10] This compound is a known *in vitro* metabolite of norephedrine,[10,11] but to our knowledge has not been isolated previously in studies on amphetamines.

The present study, and results from other investigations[1,12–16] permits a postulation of the mechanisms involved in the formation of the *in vitro* metabolites of NMA in rats (Scheme 5). 1-Phenyl-2-propanol (**1g**) was not detected in the rat experiments. A previous study[17] on the *in vitro* metabolism of *N*-*n*-propylamphetamine also demonstrated the inability of fortified rat liver homogenates to further metabolize 1-phenyl-2-propanone to 1-phenyl-2-propanol (**1g**). Investigations are still in progress to determine whether the nitrone **1c** is formed chemically or metabolically from *N*-hydroxy-NMA (**1b**), or via some other intermediate. The *in vitro* metabolism of 1-phenyl-2-propanone (**2c**) in rat liver homogenates is also under investigation. Preliminary results indicate that several metabolites are formed including 1-hydroxy-1-phenyl-2-propanone (**2d**).

Using the techniques similar to those employed in the *in vitro* rat liver study, the following metabolites were formed and identified when NMA was incubated with fortified rabbit liver homogenates: *N*-hydroxy-NMA (**1b**), the *N*-methylene nitrone (**1c**), amphetamine (**1e**), 1-phenyl-2-propanone (**2c**), 1-phenyl-2-propanol (**1g**) and trace amounts of *N*-hydroxyamphetamine (**1d**) and 1-phenyl-2-propanone oxime (**2b**). However, neither 2-nitro-1-phenylpropane (**1f**) nor 1-hydroxy-1-phenyl-2-propanone (**2d**) was detected by GC.

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