Mass Spectral Characterization of Doxylamine and its Rhesus Monkey Urinary Metabolites

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This study describes the use of mass spectrometry (MS), high-performance liquid chromatography (HPLC) and chemical derivatization techniques for the identification of doxylamine and five rhesus monkey urinary metabolites. The analyses were performed using chemical ionization mass spectrometry with either methane or ammonia as the reagent gas. The confirmation of the structures of two of these urinary metabolites was aided by the synthesis of doxylamine *N*-oxide and desmethyldoxylamine and by the use of methylation and acetylation derivatization techniques. Doxylamine *N*-oxide, desmethyldoxylamine, didesmethyldoxylamine, and two metabolites which resulted from the cleavage of the aliphatic tertiary nitrogen side chain to the subsequent 2-[1-phenyl-1-(2-pyridinyl)ethoxy]acetic acid or 2-[1-phenyl-1-(2-pyridinyl)ethoxy]methanol compounds were isolated and identified from rhesus monkey urine. Additional data concerning the mass spectral analysis of derivatization or reaction products from the three chloroformate reactions with doxylamine, and the synthesis and separation techniques which afforded mass spectral identification of the urinary metabolites are also presented.

INTRODUCTION

The antihistamine doxylamine succinate, *N*,*N*-dimethyl-2-[1-phenyl-1-(2-pyridinyl)ethoxy]ethanamine succinate, is a component in Bendectin®, a product previously prescribed to pregnant women for symptoms of nausea and vomiting, and in over-the-counter sleep-aids and other pharmaceutical products widely used in the United States since 1948.[1-5] Previous studies with rabbits and rats,[6] and with pregnant women,[7] reported no evidence of fetal malformations occurring with exposure to Bendectin®. However, recent studies in non-human primates dosed with Bendectin® during organogenesis have shown an increase in cardiac ventricular septal defects in fetuses examined at 100 days of gestation.[8,9] Moreover, Althaus *et al.*[10] reported DNA damage induced by methapyrilene. Methapyrilene, an antihistamine structurally related to doxylamine, has been reported to be a rat liver carcinogen.[11] In addition, it has been reported that doxylamine succinate increased unscheduled DNA synthesis in primary cultures of rat hepatocytes.[12] A biotransformation study with doxylamine in man indicated that several possible metabolic pathways could be followed. The major urinary component was unchanged doxylamine (60%) and five minor metabolites were also reported at much smaller percentages (<10%).[13]

Earlier studies with doxylamine succinate and other related antihistaminic drugs used either non-specific colorimetric methods or relied on thin layer chromatographic (TLC) and infrared spectral (IR) analyses to isolate or identify[14-16] the urinary products. In view of the paucity of information concerning the metabolism or excretion pattern of doxylamine, we studied the metabolic fate of this drug after its administration in Bendectin® to rhesus monkeys.

This report describes the identification of doxylamine and five urinary metabolites from the rhesus monkey using chemical ionization (CI) mass spectrometry. High-performance liquid chromatography (HPLC) was used for the separation of the metabolites, and a combination of methylation or acetylation of the isolated metabolites was used in the subsequent structural characterization of doxylamine and its related metabolites by mass spectrometry. A description of the synthesis of two urinary metabolites, doxylamine *N*-oxide and desmethyldoxylamine, is also presented.

EXPERIMENTAL

Instrumental

The IR analyses of doxylamine (**1**), doxylamine *N*-oxide (**2**) and desmethyldoxylamine (**3**) were conducted with a Pye Unicam 3-100 infrared spectrophotometer (Sargeant-Welch, Dallas, Texas) as neat films on NaCl plates. Standards of **1**, **2**, and **3** were also characterized by hydrogen nuclear magnetic resonance (NMR) spectrometry using a Bruker WH-500 spectrometer operated at 500 MHz. A Finnigan 4023 gas chromatographic/mass spectrometric data system (San Jose, California) was used in either the CH_4 CI or NH_3 CI mode with a Vacumetrics (Ventura, California) desorption chemical ionization (DCI) probe incorporating a platinum filament; a heating ramp of 60 s was used for the mass spectrometric analyses. A Spectra Physics SP 8700 high-performance liquid chromatographic (HPLC) system (Houston, Texas) with a Supelcosil LC18 (5 μm,

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250 mm × 4.6 mm i.d.) column and a Hewlett-Packard 1040 A (Memphis, Tennessee) detector was used.

Reagents and chemicals

Bendectin® tablets (Merrell Dow Pharmaceuticals), containing 10 mg of doxylamine succinate and 10 mg pyridoxine hydrochloride, were used as received. Doxylamine succinate and [^{14}C]doxylamine succinate (custom made by Southwest Foundation for Research and Education, San Antonio, Texas) were assayed by HPLC and showed no extraneous peaks, indicating that the purity was essentially 100%. Mass spectrometry and NMR spectral analysis of the test chemical after conversion to the free amine were consistent with the structure of doxylamine (Table 1). The basic alumina and silica gel was used as received to prepare the gravity clean-up columns. All solvents were UV grade and all reagents were CP grade.

Synthesis and purification of doxylamine *N*-oxide and desmethyldoxylamine

Doxylamine *N*-oxide (2). The synthetic method for the doxylamine *N*-oxide standard incorporated the procedure used by Chaudhuri *et al.*[17] for the preparation of tripelennamine *N*-oxide, a similarly structured antihistamine. A sample of doxylamine succinate (1.437 g (3.7 mmol) equivalent to 1 g of doxylamine free amine) was weighed into a 50 ml culture tube and 25 ml of deionized water and 2 ml of 10 N sodium hydroxide were added. The sample was then extracted with 3 × 25 ml of dichloromethane and each subsequent dichloromethane portion was percolated through a plug of anhydrous sodium sulfate into a 100 ml round-bottom flask. The dichloromethane fraction was then evaporated to dryness by water pump aspiration at ambient temperature. The residue (oil) which contained **1** was redissolved in 10 ml of dichloromethane and quantitatively transferred to a 30 ml culture tube containing 0.8 g (4.6 mmol) of *m*-chloroperoxybenzoic acid, sealed with a Teflon-lined screw cap and allowed to react for 2 h at ambient temperature. The reaction was stopped by allowing the sample to percolate through a basic alumina column (20 g, prewashed with 20 ml of dichloromethane). The unchanged **1** eluted in the initial 5 ml of solvent and **2** was eluted from the column as a yellow band with three 5 ml portions of methanol. The yield of **2** was 80% and a 1 mg ml^{-1} standard was prepared for analysis of purity by HPLC. The results showed a purity of greater than 99%. The NMR, IR and mass spectral analyses were consistent with the structure for **2** indicated in Table 1.

Desmethyldoxylamine (3). The method for the preparation of **3** was a procedure developed by Olofson *et al.*[18] for the selective *N*-dealkylation of tertiary amines. Doxylamine succinate (1.437 g, 3.7 mmol) was prepared as the doxylamine (free amine) as described for the synthesis of **2**. The doxylamine free amine in 5 ml of dichloroethane was slowly added in drops to a 125 ml flat-bottom flask containing a stirring bar, 10 ml of vinyl chloroformate and 20 ml of dichloroethane which had been cooled in an ice bath for 20 min. A milky white phase was formed during the addition which contained doxylamine vinyl chloroformate (**13**). The flask was allowed to reach ambient temperature and the contents of the flask refluxed for 30 min. After the flask was cool the contents of the flask were evaporated to dryness by water pump aspiration. The residue (solid), **13**, was stored in a freezer (−5 °C) overnight. The sample **13** was redissolved in 20 ml of 1 N HCl and transferred to a 50 ml culture tube, sealed with a Teflon-lined screw cap and the contents heated at 85 °C for 30 min. The culture tube was cooled to ambient temperature and 2.1 ml of 10 N sodium hydroxide was added to adjust the pH to 12. The contents of the tube were extracted with two 20 ml portions of dichloromethane and the extracts were combined in a 100 ml round-bottom flask and evaporated to dryness. A 43% yield of **3** was obtained. The quantitative standard (1.5 mg ml^{-1} in methanol) purity of **3** was determined by HPLC to be greater than 99% and the NMR, IR and mass spectral analyses were consistent with the structure for **3** indicated in Table 1.

Derivatization techniques

Acetylation. The acetylation of both **3** and the alcohol metabolite of doxylamine, [1-phenyl-1-(2-pyridinyl)-ethoxy]methanol (**9**), was achieved using acetic anhydride (>99%) in pyridine. The following procedure was used. The samples in methanol (1 ml) were pipetted into an 8 ml culture tube containing 50 µl of pyridine and 250 µl of acetic anhydride, the tube was sealed with a Teflon-lined screw cap and the contents allowed to react for 2 h. The contents of the tube were then evaporated under dry nitrogen at ambient temperature.

Methylation. The acid metabolite of doxylamine, 2-[1-phenyl-1-(2-pyridinyl)ethoxy]acetic acid (**7**), was methylated with gaseous diazomethane. The gas was generated in an apparatus containing 2 ml of 60% potassium hydroxide, 1 ml of 2(2-ethoxyethoxy)ethanol and 1 ml of anhydrous ethyl ether, to which 0.5 g of Diazald® was added. The urinary metabolite was dissolved in 1 ml of methanol in an 8 ml culture tube and gaseous diazomethane was passed through a glass disposable Pasteur pipette into the sample until a persistent yellow color was observed. A gentle nitrogen flow through the apparatus was used to purge the system of any remaining gaseous diazomethane.

High-performance liquid chromatographic (HPLC) system

An isocratic HPLC system was developed to achieve resolution of doxylamine (**1**) and the two synthesized compounds **2** and **3** and to monitor the synthesis reaction steps and derivatization techniques to be used with the urinary metabolites. The HPLC system consisted of a Spectra Physics SP 8700 solvent programmer (Houston, Texas) operated isocratically with a Rheodyne model 7125 septumless injector (Berkeley, California), a Supelcosil LC18 column (5 µm, 250 mm × 4.6 mm i.d.) and a Hewlett-Packard 1040 A ultraviolet detector system operated at 254 nm. The mobile phase consisted of 90% methanol–10% potassium phosphate monobasic buffer

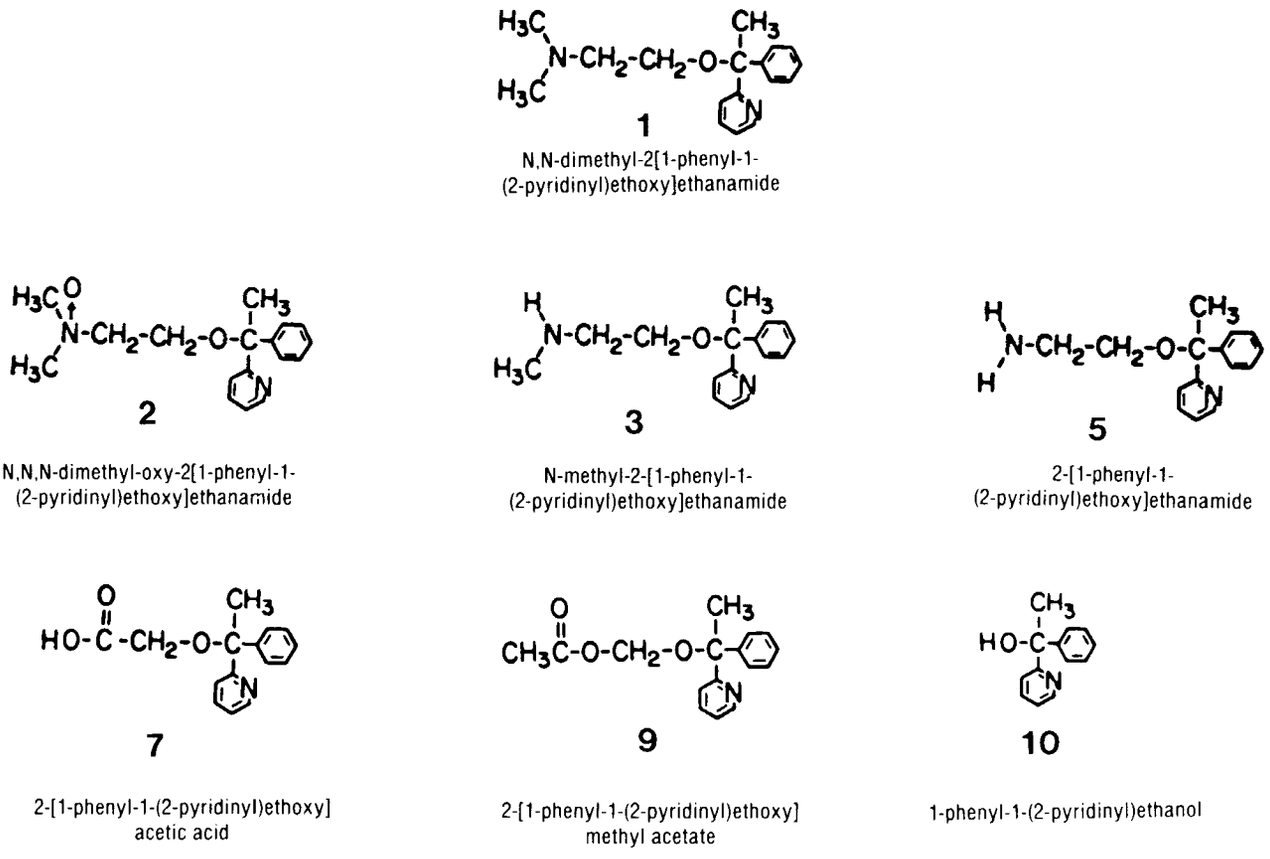

Figure 1. Structures and IUPAC names for doxylamine related compounds.

(0.01 M, pH 7) which flowed at a rate of 1.0 ml min^{-1} and a pressure of 1500 psi. All injection volumes were in 10 μl of methanol. The retention times (t_R) for **1**, **2** and **3** were 5.8, 4.0 and 11.8 min, respectively.

Preparation of dose and urine collection

The dose solutions were prepared to contain 13.3 mg kg^{-1} of Bendectin® and 80–200 μCi (32.5 μCi $mmol^{-1}$) [^{14}C]doxylamine succinate for each of the three adult, female rhesus monkeys used in the studies.[19,20] Since the Bendectin® was formulated into tablets, these tablets were pulverized into a fine powder, suspended in distilled water with the [^{14}C]doxylamine succinate and administered to the animals by gastric intubation. Each Bendectin® tablet contains 10 mg each of doxylamine succinate and pyridoxine hydrochloride held together with the appropriate inert excipients and coatings.

The rhesus monkey urine was collected over dry ice 12 h before the drug was administered, and from 0–6, 6–24 and 24–48 h after administration. Homogeneous 100 ml aliquots were frozen at −20 °C until analysis and the volume of urine excreted was recorded for each animal.

RESULTS AND DISCUSSION

In order to identify the chemical structures of the rhesus monkey urinary metabolites of doxylamine by mass spectrometry, the analytical standards (compounds **1**, **2** and **3**) were characterized by IR, mass spectrometry, NMR spectroscopy and chemical derivatization analytical techniques (Fig. 1). The results from the assays by these techniques with the synthesized standards were consistent with their chemical structures and agreed with the information available from the literature concerning these compounds.[13,21] The mass spectra of doxylamine using both the electron impact (EI) and chemical ionization (CI) conditions are shown in Fig. 2. The absence of an observable molecular ion in the analysis of doxylamine (Fig. 2(a)) showed that EI mass spectrometry had limited usefulness as a structural identification technique for either doxylamine or its related urinary metabolites. The mass spectra obtained for doxylamine by chemical ionization (CI) using methane or ammonia reagent gas were found to provide both an $[M+1]^+$ ion and one major fragment ion, as shown in Figs 2(b) and 2(c). Under CI mass spectrometric conditions the major fragment ion for doxylamine was found to be m/z 182 with methane as the reagent gas and m/z 184 with ammonia as the reagent gas. The fragment ion m/z 184 was found to be a useful marker for doxylamine and its related metabolites when analysing rhesus monkey urine extracts under ammonia CI mass spectrometric conditions. The mechanism for the formation of this major doxylamine fragment ion (m/z 184) is discussed elsewhere.[22]

The mass spectral results obtained for compound **1**, its related urinary metabolites and other intermediate reaction products following derivatization are summarized in Table 1. Under ammonia CI mass spectrometric

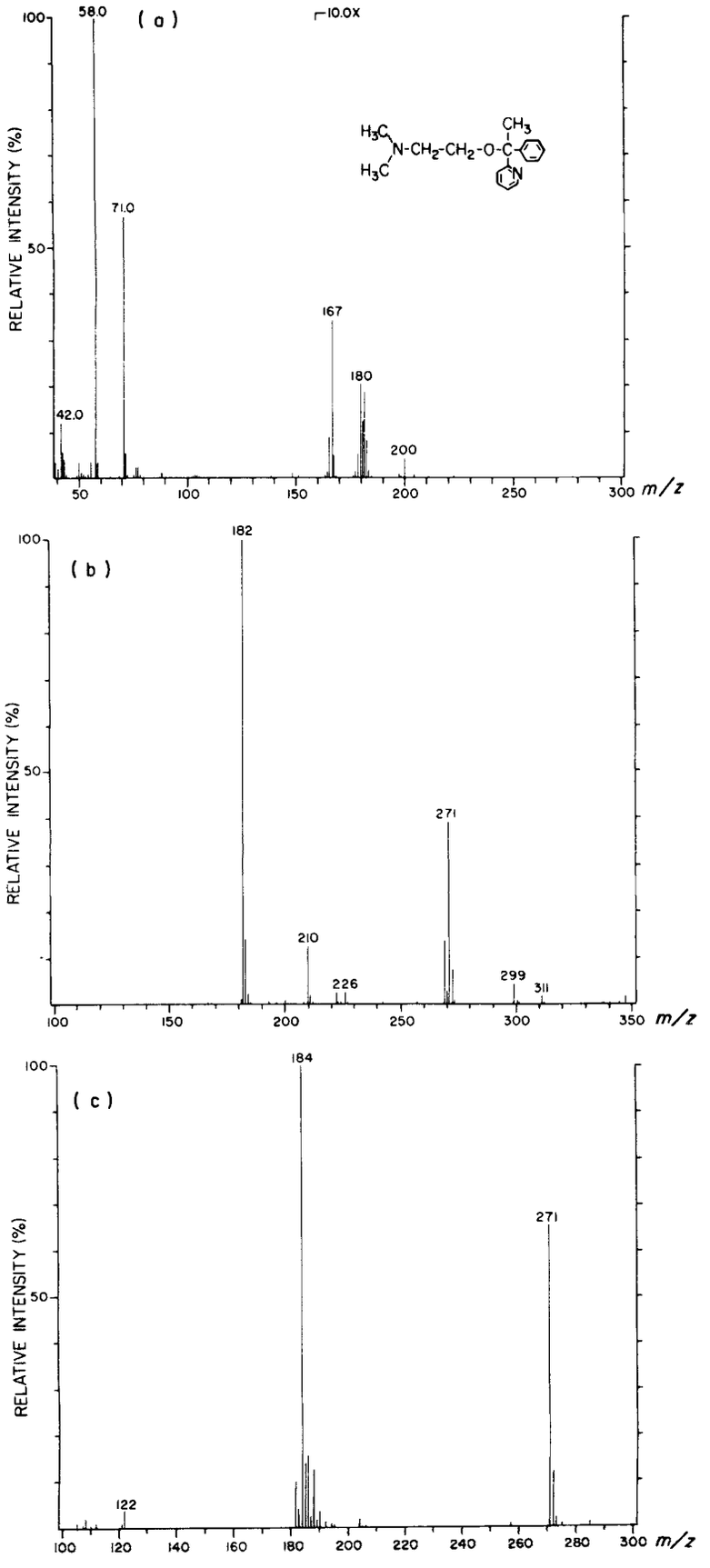

Figure 2. (a) EI, (b) methane and (c) ammonia CI mass spectrum of doxylamine.

Table 1. Relative ion abundances (%) of recovered doxylamine, its related metabolites, subsequent derivatization products and related synthesized compounds in positive ion chemical ionization mass spectrometry (methane or ammonia reagent gas)[a,b]

No.	Compound	Formula	Molecular weight	Relative abundances (%)			
				Methane CI		Ammonia CI	
				$[M+1]^+$	m/z 182	$[M+1]^+$	m/z 184
1	Doxylamine, unchanged	$C_{17}H_{22}N_2O$	270	30	100	10	100
2	Doxylamine *N*-oxide, metabolite	$C_{17}H_{22}N_2O_2$	286	13	100	15	100
3	Desmethyldoxylamine, metabolite	$C_{16}H_{20}N_2O$	256	20	100	30	100
4	Acetylated desmethyldoxylamine	$C_{18}H_{22}N_2O_2$	298	10	100	100	75
5	Didesmethyldoxylamine, metabolite	$C_{15}H_{18}N_2O$	242	—	—	100	57
6	Acetylated didesmethyldoxylamine	$C_{17}H_{20}N_2O_2$	284	—	—	100	41
7	Acid metabolite, 2-[1-phenyl-1-(2-pyridinyl)ethoxy]acetic acid	$C_{15}H_{15}NO_3$	257	—	—	100	79
8	Methyl ester of acid metabolite, 2-[1-phenyl-1-(2-pyridinyl)ethoxy]methyl acetate	$C_{16}H_{17}NO_3$	271	—	—	100	35
9	Acetylated alcohol metabolite, 2-[1-phenyl-1-(2-pyridinyl)ethoxy]methanol	$C_{16}H_{17}NO_3$	271	—	—	100	36
10	Carbinol, 1-phenyl-1-(2-pyridinyl)ethanol	$C_{13}H_{13}NO$	199	20	100	100	23
11	Doxylamine ethyl chloroformate	$C_{19}H_{24}N_2O_3$	328	—	—	100	38
12	Doxylamine 2,2,2-trichloroethyl chloroformate	$C_{19}H_{21}Cl_3N_2O_3$	430	—	—	32	100
13	Doxylamine vinyl chloroformate	$C_{19}H_{22}N_2O_3$	326	25	100	—	—

[a] Relative abundances are normalized to 100% for the base peak of the spectrum.
[b] Only the $[M+1]^+$ ion and the 'doxylamine marker ion', m/z 182 for methane reagent gas and m/z 184 for ammonia reagent gas are listed in this table.

conditions, the m/z 184 ion was found to be a major fragment ion for each of the compounds analysed in this study. Therefore m/z 184 was used as a 'doxylamine marker ion' to aid in the detection of doxylamine related metabolites in rhesus monkey urine extracts. The $[M+1]^+$ ion for metabolite **2** was observed at m/z 287 and the structure and CI mass spectrum of the synthesized standard is shown in Fig. 3. The NMR spectrum of the *N*-oxide of doxylamine as compared to doxylamine indicated that the *N*-oxide was on the aliphatic nitrogen and not on the pyridyl ring. This was shown by the absence of change in the aromatic region which would be expected for a pyridyl *N*-oxide and by the presence of a downfield shift noted for the CH_2 proton adjacent to the aliphatic nitrogen ($\approx 2.6\delta \rightarrow 3.2\delta$). Also, the m/z 184 fragment for the *N*-oxide of doxylamine by ammonia CI mass spectrometry shows no substitution of the aromatic end of the molecule. The $[M+1]^+$ ion of metabolite **3** produced by ammonia CI mass spectrometry was observed at m/z 257 and after acetylation

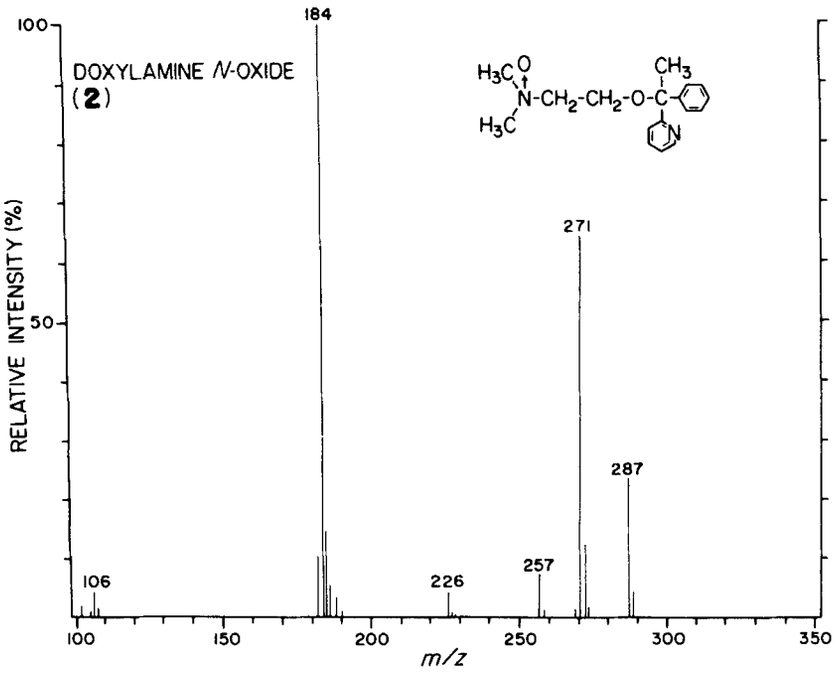

Figure 3. Ammonia CI mass spectrum of synthesized doxylamine *N*-oxide.

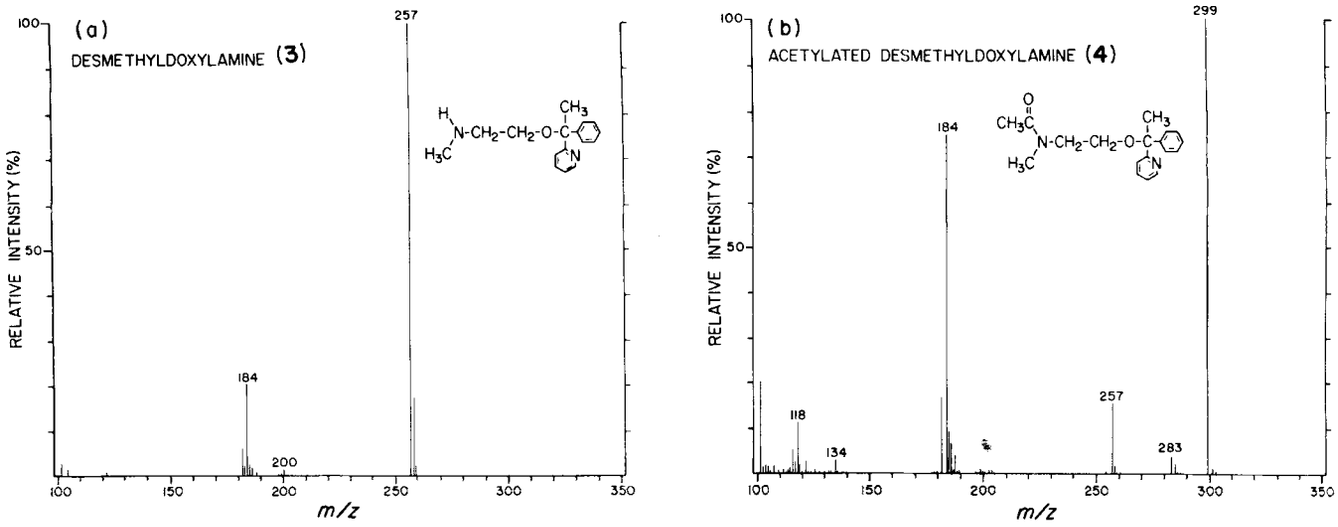

Figure 4. Ammonia CI mass spectrum of synthesized (a) desmethyldoxylamine and (b) acetylated desmethyldoxylamine standards.

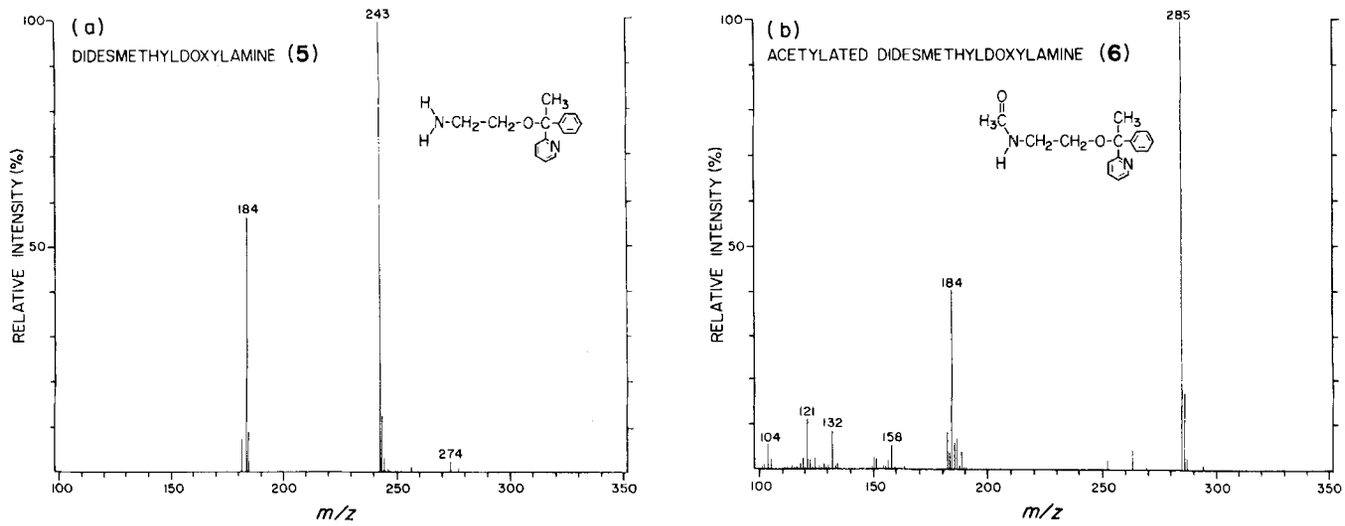

Figure 5. Ammonia CI mass spectrum of (a) didesmethyldoxylamine metabolite and (b) the metabolite didesmethyldoxylamine after acetylation.

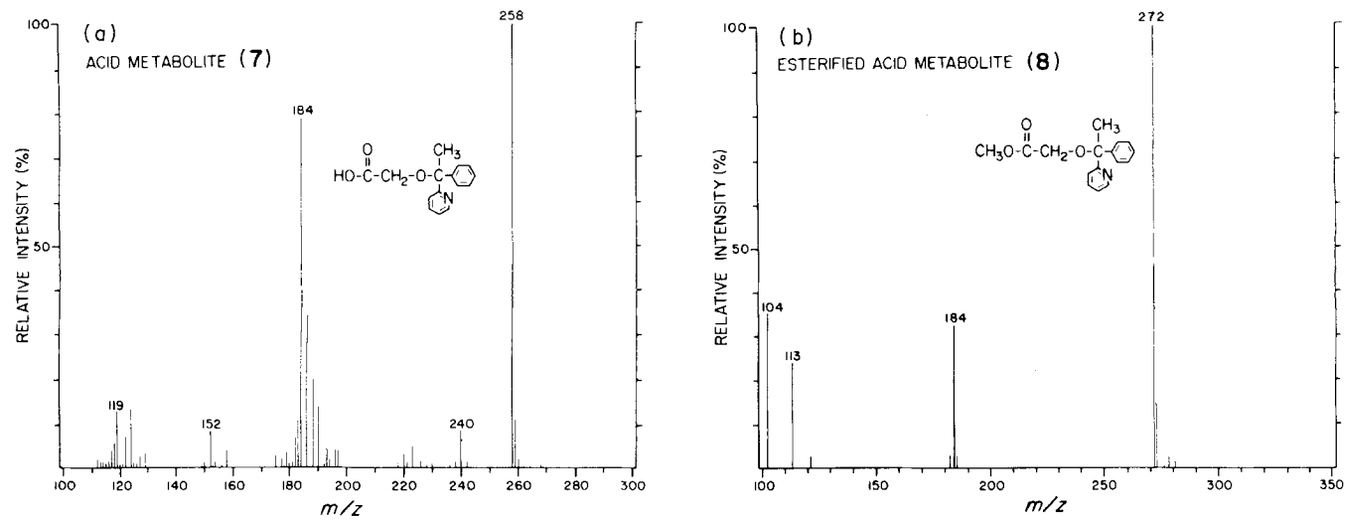

Figure 6. Ammonia CI mass spectrum of (a) the acid metabolite and (b) the esterified acid metabolite.

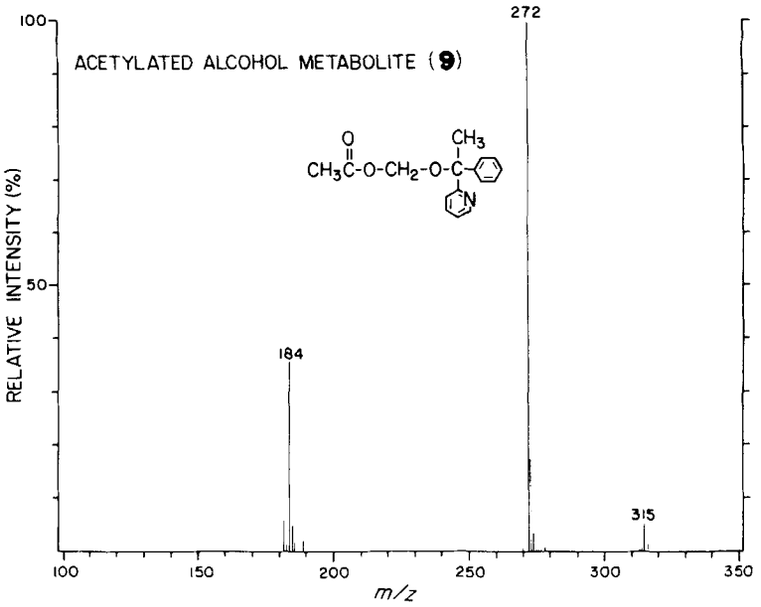

Figure 7. Ammonia CI mass spectrum of the acetylated alcohol metabolite.

with acetic anhydride was shifted to m/z 299. The results of the CI mass spectra for **3** and **4** synthesized standards are shown in Fig. 4 and when compared to the unknown metabolite spectrum indicate that metabolite **3** was desmethyldoxylamine. The NMR spectrum of **3** as compared with that of doxylamine showed few changes other than the loss of intensity for the N—CH_3 protons and a downfield shift as expected for a change from the tertiary amine to that of a secondary amine. The ammonia CI mass spectrum indicates the same fragmentation pattern for the aromatic portion of the molecule. The ammonia CI mass spectrum of the metabolite **5** showed the $[M+1]^+$ ion at m/z 243 and after acetylation with acetic anhydride the observed $[M+1]^+$ ion was at m/z 285. These results are shown in Fig. 5 and indicate that compound **5** was didesmethyldoxylamine.

The acid metabolite **7** and the alcohol metabolite **9** of doxylamine accounted for approximately 27% of the administered dose, and required the derivatization techniques of acetylation and esterification to establish separation by HPLC since they co-eluted in the underivatized form. The acid metabolite of doxylamine, **7**, showed an ammonia CI mass spectrum with an $[M+1]^+$ ion at m/z 258. After esterification of the metabolite **7** with gaseous diazomethane the methyl ester, **8**, was obtained with an $[M+1]^+$ ion at m/z 272. The CI mass spectra for compounds **7** and **8** are shown in Fig. 6. The alcohol metabolite of doxylamine, **9**, after acetylation with acetic anhydride produced an $[M+1]^+$ ion at m/z 272, and its mass spectrum is shown in Fig. 7 together with its chemical structure.

The 1-phenyl-1-(2-pyridinyl)ethanol (**10**) was synthesized by Dr James Althaus of our laboratory for use as an analytical standard, since it had been previously reported as a possible urinary metabolite of doxylamine.[13] However, this compound, **10**, was not found in the urine of the rhesus monkey. Three *N*-dealkylating reagents were used in the preparation of compound **3**; these three reagents resulted in the preparation of compounds **11**, **12** and **13**. The doxylamine vinyl chloroformate (**13**) proved to be readily hydrolysed to compound

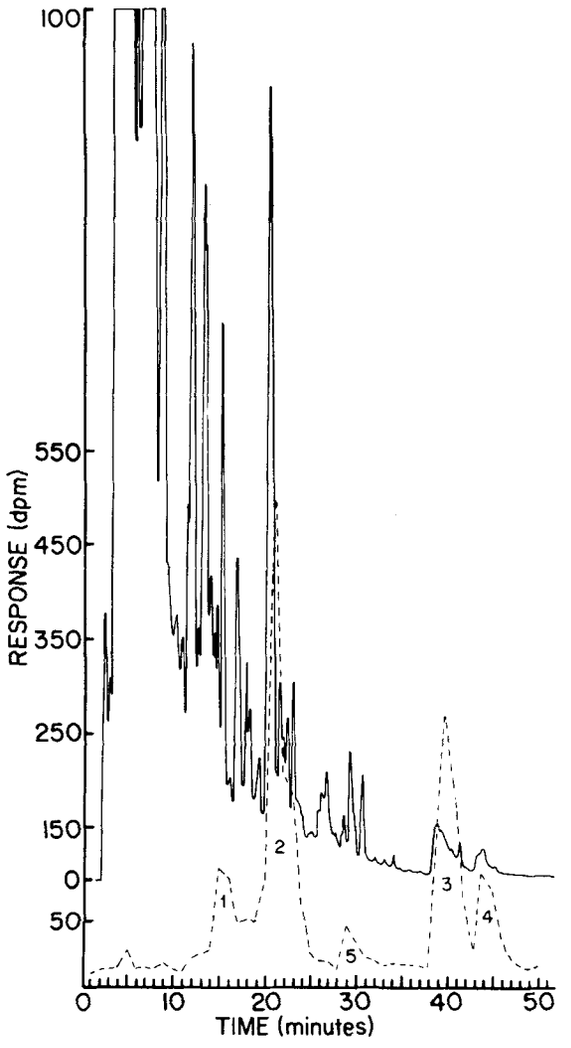

Figure 8. An HPLC gradient chromatogram (UV at 254 nm) of urine from a rhesus monkey dosed with [^{14}C]doxylamine succinate. The solid lines represent a 20 μl injection of a 1 ml sample of monkey urine (21–24 hours) at a sensitivity of 2.0 AUFS. The broken lines (superimposed) illustrate the response in dpm of the ^{14}C-labeled urinary metabolites.

3 by mild acid hydrolysis (1 N HCl), with a satisfactory yield of 43%. However, the two other *N*-dealkylated intermediate reaction products, **11** and **12**, were more difficult to convert to the desired *N*-desmethyldoxylamine, with less than 10% recovered after the mild acid hydrolysis.

In conclusion, the analytical method used—isolation of the urinary metabolites by HPLC, followed by the chemical derivatization techniques of acetylation and esterification, and finally the use of the fragment ion marker (m/z 184) present in all the compounds assayed under CI mass spectrometry (ammonia reagent gas)—provided the conditions necessary for the identification of doxylamine and its metabolites which represented approximately 70% of the administered dose in rhesus monkey urine.[19] The analysis of a rhesus monkey urine fraction (21–24 h) collected from animals dosed with [^{14}C]doxylamine succinate at 20 times the normal human dose is shown in Fig. 8. The urine contained an unknown doxylamine conjugate (peak 1), the acid and alcohol metabolites (peak 2), doxylamine and didesmethyldoxylamine which also co-elute (peak 3), desmethyldoxylamine (peak 4), and the *N*-oxide of doxylamine (peak 5). The isolated urinary metabolites of doxylamine, **3** and **5**, have been previously reported.[13] Metabolite **7**, the acidic side-chain oxidation product, has been previously mentioned as a human urinary metabolite of doxylamine, but no mass spectral characterization data were presented.[23] However, compound **2** (doxylamine *N*-oxide) and the polar metabolite **9**, which resulted from the cleavage of the aliphatic tertiary nitrogen side chain to the subsequent alcohol, have not previously been reported for doxylamine.

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