3-Methyl-6-isopropylcyclohexen-1-yl diethyl phosphate (7): 40% yield; bp 103–108 °C (1.0 mm); IR (neat) 1664, 1290, 1270, 1000, 838 cm^{-1}; NMR (CCl_4) δ 0.65–1.15 (m 10 H), 1.32 (t, 6 H), 1.54–2.54 (m, 6 H), 4.02 (2 q, 4 H), 5.28 (m, 1 H).

Anal. Calcd for $C_{14}H_{27}O_4P$: C, 57.92; H, 9.37; P 10.67. Found: C, 57.67; H, 9.28; P, 9.96.

2,6-Dimethoxy-4-(2-pentenyl)phenyl diethyl phosphate (14): 97% yield; bp 180–182 °C (0.55 mm); IR (neat) 1598, 1275, 1220, 1163, 1130, 1028, 818 cm^{-1}; NMR (CCl_4) δ 0.97 (t, 3 H), 1.32 (t, 6 H), 2.00 (m, 2 H), 3.17 (m, 2 H), 3.71 (s, 6 H), 4.10 (2 q, 4 H), 5.39 (m, 2 H), 6.20 (s, 2 H).

Anal. Calcd for $C_{17}H_{27}O_6P$: C, 56.98; H, 7.59; P, 8.64. Found: C, 56.89; H, 7.74; P, 8.38.

Electroreduction of Diethyl Phosphates (4, 7, 9, 14, 16-22). A solution of 3.3 mmol of a phosphate in 30 mL of commercial DMF containing 5 g of Et_4NOTs was electrochemically reduced at the cathode potential of −2.6 to −2.7 V vs. SCE in a divided cell equipped with a platinum anode and a lead cathode. During the reaction, the solution was stirred with a magnetic stirrer and cooled with running water. After the amount of electricity listed in Table I was passed, the reaction mixture was poured into 100 mL of cold 3% aqueous hydrochloric acid, and organic products were extracted with three 50-mL portions of ether. The combined ethereal solution was dried over anhydrous magnesium sulfate, filtered, and evaporated to give the products in the yields shown in Table I. Products other than *m-n*-propylanisole, **8**, and **15** were identified by their physical and spectroscopic comparison with those of commercially available authentic samples. Product **8** was identified spectroscopically by comparison with the authentic sample.[12] The spectroscopic data of **15** were completely identical with those in the literature.[13] An analytical sample of *m-n*-propylanisole was collected by preparative GLC: IR (neat) 3060, 3030, 3000, 1610, 1585, 1262, 1045, 875, 775, 695 cm^{-1}; NMR (CCl_4) δ 0.91 (t, 3 H), 1.62 (m 2 H), 2.51 (t, 2 H), 3.69 (s, 3 H), 6.37–6.70 (m 3 H), 6.83–7.17 (m, 1 H); MS, *m/e* 150 (M^+).

Electroreduction of 9 in (a) a Dry DMF–D_2O System and (b) a DMF-d_7–D_2O System. (a) Commercial DMF was dried over calcium hydride, and the upper layer (300 mL) was decanted into a distillation flask containing D_2O (2 mL) and dry benzene (50 mL). The solution was distilled under a dry nitrogen stream at reduced pressure. DMF was distilled at the boiling point of 30–40 °C (1–5 mm), whereas D_2O and benzene were collected as a first fraction in a trap cooled with dry ice–acetone. This procedure was repeated twice. A solution of 0.25 mmol of **9** in 1 mL of dry DMF containing 0.15 g of anhydrous Bu_4NClO_4 and 6 μL of D_2O was electrochemically reduced in a divided cell equipped with a platinum anode and a lead cathode under a dry nitrogen stream. After 8 F/mol of electricity was passed, the usual workup yielded a mixture of **10** and **10′**. The isotopic purity (60 ± 10%) was calculated from NMR spectra of the product. (b) The electrolysis using commercial DMF-d_7 (99% grade) and anhydrous $LiClO_4$ was performed in a similar way as above.

2,6-Dimethoxyphenyl 2-Pentenyl Ether (12). A solution of 11.68 g (75 mmol) of pyrogallol 1,3-dimethyl ether and 13.3 g (89 mmol) of 1-bromo-2-pentene in 50 mL of acetone containing 13.5 g (97.5 mmol) of potassium carbonate was refluxed for 10.5 h. To the cooled solution was added 100 mL of water, and the solution was extracted with four 25-mL portions of ether. The ethereal solution was washed with two 50-mL portions of 10% sodium hydroxide solution and 30 mL of saturated brine and dried over calcium chloride; the solvent was evaporated. Distillation of the residual oil gave 14.58 g (88%) of compound **12**: bp 112–115 °C (1.0 mm); IR (neat) 3000, 1595, 1115, 970, 775, 732 cm^{-1}; NMR (CCl_4) δ 0.98 (t, 3 H), 2.00 (m, 2 H), 3.73 (s, 6 H), 4.27 (m, 2 H), 5.60 (m, 2 H), 6.3–6.9 (m, 3 H).

Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.47; H, 8.11.

5-(2-Pentenyl)pyrogallol 1,3-Dimethyl Ether (13). The conversion of **12** to **13** was carried out by the method of Hahn and Wassmuth:[14] 75% yield; bp 126–135 °C (0.6 mm); IR (neat) 3500, 3025, 3000, 1615, 1115, 970, 835 cm^{-1}; NMR (CCl_4) δ 0.99 (t, 3 H), 2.06 (m, 2 H), 3.16 (m, 2 H), 3.79 (s, 6 H), 4.96 (s br, 1 H), 5.42 (m, 2 H), 6.21 (s, 2 H).

Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.02; H, 8.22.

Olivetol was obtained from **15** by the known methods.[6]

Registry No. **4**, 71774-92-0; **7**, 71774-93-1; **9**, 71774-94-2; **10**, 71786-23-7; **10′**, 62103-69-9; **11**, 91-10-1; **12**, 71774-95-3; **13**, 71774-96-4; **14**, 71774-97-5; **15**, 22976-40-5; **16**, 16463-00-6; **17**, 67951-84-2; **18**, 26057-16-9; **19**, 71774-98-6; **20**, 67951-87-5; **21**, 71774-99-7; **22**, 16519-26-9; anisole, 100-66-3; *p*-cymene, 99-87-6; *m*-dimethoxybenzene, 151-10-0; tetralin, 119-64-2; tetrahydro-2-furanmethanol, 97-99-4; *trans*-3-methyl-6-isopropylcyclohex-1-en-1-ol, 71775-00-3; 2-methoxy-4-propylphenol, 2785-87-7; 2-methoxyphenol, 90-05-1; 2-isopropyl-5-methylphenol, 89-83-8; 2-methoxy-4-(2-propenyl)-phenol, 97-53-0; 2-methoxy-4-(1-propenyl)phenol, 97-54-1; 3,5-dimethoxyphenol, 500-99-2; 2-naphthol, 135-19-3; diethyl phosphate, 762-04-9; 1-bromo-2-pentene, 20599-27-3; olivetol, 500-66-3.

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Oxidation of Nitrosamines. 1. Formation of *N*-Nitrosoimminium Ions through the Oxidative Decarboxylation of *N*-Nitrosoproline, *N*-Nitrosopipecolic Acid, and *N*-Nitrososarcosine

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α-Acetoxy-*N*-nitrosopyrrolidine (**3**), α-acetoxy-*N*-nitrosopiperidine (**7**), and *N*-(α-acetoxymethylene)-*N*-methylnitrosamine (**15**), model compounds important in the study of nitrosamine metabolism, were synthesized from the corresponding nitrosamino acids. The nitrosamino acids were decarboxylated with lead tetraacetate to nitrosamino radicals, which were then oxidized to nitrosoimminium ions. Decarboxylation of nitrosoproline gave the solvolysis product **3** exclusively; nitrososarcosine gave the expected α-acetoxy compound, but dimethylnitrosamine was also obtained. Nitrosopipecolic acid gave the following compounds, with the relative yields in parentheses: *N*-nitroso-1,2,3,4-tetrahydropyridine (**8**, 10.6%), *N*-nitroso-1,2,3,6-tetrahydropyridine (**9**, 5.7%), *N*-nitroso-α-acetoxypiperidine (**7**, 33%), *N*-nitroso-*cis*-2,3-diacetoxypiperidine (**10**, 22%), *N*-nitroso-*trans*-2,3-diacetoxypiperidine (**11**, 28%), *N*-nitroso-4-acetoxy-1,2,3,4-tetrahydropyridine (**13**, <1%). The product distribution from the decarboxylation experiments is attributed to the stability of the nitrosoimminium ions.

The metabolic activation of nitrosamines to proximate carcinogens through α-hydroxylation has received much attention.[1] It is suggested that the highly reactive hydroxylated nitrosamine breaks down to a hydroxyazo in-

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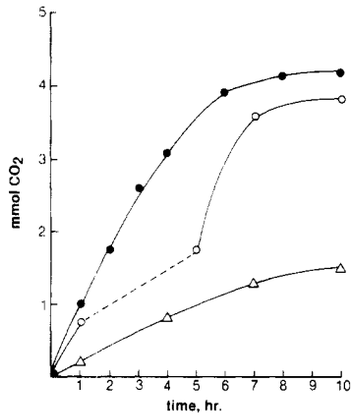
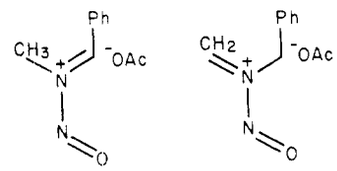


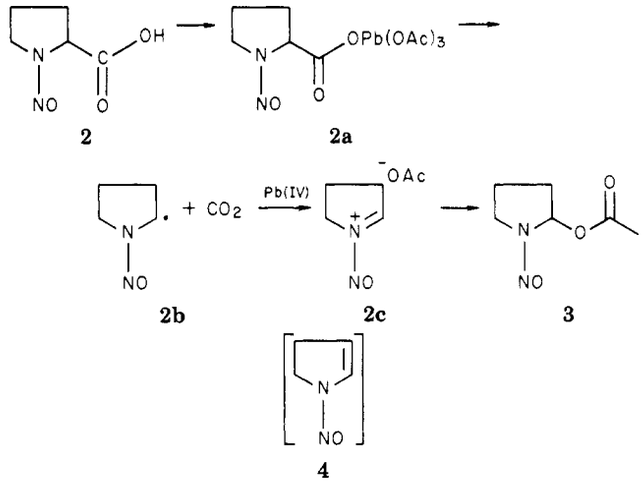
Figure 1. Oxidative decarboxylation of *N*-nitrosoproline without pyridine at 40 °C, △. Pyridine–catalyzed decarboxylation at 40 °C under N_2, ●. Catalyzed decarboxylation under O_2, O---O; continued under N_2, O—O.

termediate which upon loss of nitrogen forms an alkylating agent.[2] Recent experiments by Baldwin and co-workers[3] have demonstrated a striking difference in chemical reactivity between two structural isomers, *N*-(α-acetoxymethyl)-*N*-benzylnitrosamine and *N*-methyl-*N*-(α-acetoxybenzyl)nitrosamine. The latter compound hydrolyzed at 3 times the rate of its isomer and was a powerful bacterial mutagen.[1e] The formation of the resonance-stabilized benzyl nitrosoimminium ion **1a**, more stable than isomer **1b**, was responsible for its greater reactivity.



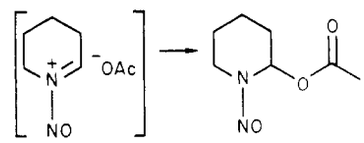
1a **1b**

These findings prompted us to study the formation of a nitrosopyrrolidinimminium ion and a nitrosopiperidinimminium ion derived from the oxidative decarboxylation of *N*-nitrosoproline (**2**) and *N*-nitrosopipecolic acid (**5**), respectively. Our results support the observations of Baldwin and co-workers[1] that not only alkyl carbocation from the hydroxyazo intermediate but also other highly electrophilic species can be formed from the α-hydroxylated nitrosamines. The synthesis of α-acetoxynitrosopyrrolidine (**3**) and α-acetoxynitrosopiperidine (**7**) from the oxidative decarboxylation of the corresponding nitrosamino acids with lead tetraacetate was reported in a previous communication;[4] however, no mechanism was given. It has been established that most acids are decarboxylated by lead tetraacetate through a free-radical chain mechanism.[5a] Therefore, the reaction of **2** with the oxidizing agent was expected to go through the lead(IV) carboxylate intermediate **2a** which would decompose to an alkyl radical **2b** and lead(III) acetate. The formation of alkenes and



2 **2a** **2b** **2c** **3** **4**

alkyl acetates from the oxidative decarboxylation of aliphatic acids is known to involve a carbonium ion or a transition state with considerable cationic character.[5] This cationic species is formed after the free radical has undergone a one-electron oxidation. To determine whether **2** and **6** followed a reaction pathway similar to that of



6 **7**

ordinary aliphatic carboxylic acids, we carried out decarboxylation studies under various conditions. Nitrosoproline gave almost exclusively the solvolysis product **3**, whereas *N*-nitrosopipecolic acid gave α-acetoxynitrosopiperidine (**7**) as a component of a complex mixture.

Results and Discussion

Decarboxylation of *N*-Nitrosoproline. Decarboxylation of **2** at 40 °C in methylene chloride under nitrogen with 1.2 equiv of lead tetraacetate produced CO_2 in a 47% yield after 27 h. A similar reaction with 1.2 equiv of pyridine gave an 89% yield of carbon dioxide in only 8 h. When oxygen was introduced into the system, the reaction was inhibited, but it continued at a normal rate as soon as the oxygen was replaced with nitrogen, as shown in Figure 1. The major component isolated from the decarboxylation of **2** was α-acetoxynitrosopyrrolidine (**3**). This indicated that the pyrrolidine radical **2b** was easily oxidized to the carbonium ion **2c**, thus preventing the formation of nitrosopyrrolidine by H-atom abstraction from the solvent. The fact that the ester was formed under these conditions and not nitrosopyrroline (**4**) or compounds derived from it, indicated that the carbonium ion was relatively stable. Electron delocalization through conjugation with the nitrosamine function probably enhanced the stability of the carbonium ion and thus favored substitution.

The catalysis by pyridine may take place through the coordination of the base to the lead(IV) nucleus,[6] thus facilitating the initial decomposition to a radical. The levorotatory nitrosamino acid **2**, $[\alpha]_D$ −188° (*c* 0.231, EtOH), gave the optically inactive solvolysis product **3**. The loss of optical activity ruled out the possibility of a

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(2) P. Skipper, S. Tannenbaum, J. E. Baldwin, and A. Scott, *Tetrahedron Lett.*, 4269 (1977).

(3) J. E. Baldwin, A. Scott, S. E. Branz, S. R., Tannenbaum, and L. Green, *J. Org. Chem.*, **43**, 2427 (1978).

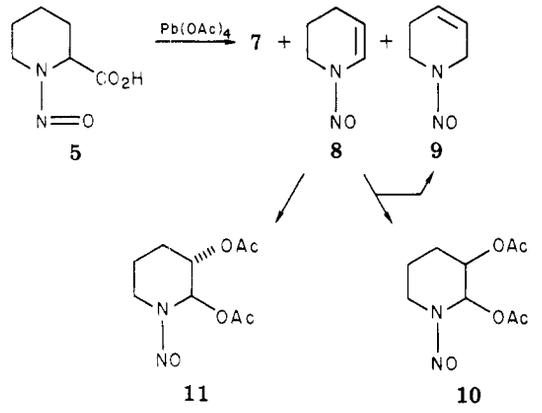
(4) J. E. Saavedra, *Tetrahedron Lett.*, 1923 (1978).

(5) (a) J. K. Kochi, *J. Am. Chem. Soc.*, **87**, 1811 (1965); (b) *Ibid.*, **87**, 3609 (1965); (c) J. K. Kochi, J. D. Bacha, and T. W. Bathea, III, *Ibid.*, **89**, 6538 (1967); (d) J. D. Bacha and J. K. Kochi, *J. Org. Chem.*, **33**, 83 (1968); (e) R. A. Shelden and J. K. Kochi, *Org. React.*, **19**, 279 (1972).

(6) R. Partch and J. Monthony, *Tetrahedron Lett.*, 4427 (1967).

concerted mechanism and indicated that the radical intermediate, or the cation, was sufficiently long-lived to undergo racemization. Alkanes are known to be side products of the decarboxylation of aliphatic acids. Their formation is inversely proportional to the ease of oxidation of the intermediate alkyl radical.[5] Since no nitrosopyrrolidine was formed from the oxidation of **2**, it is assumed that the radical **2b** is easily oxidized to the carbonium ion **2c**. Decarboxylation of **2** with lead(IV) containing cupric acetate also gave exclusively the solvolysis product **3**. This reaction was slow compared with that catalyzed by pyridine. The yield of carbon dioxide was only 40% after 58 h at 40 °C. It is apparent from these results that cupric acetate had little or no effect on the decarboxylation of nitrosoproline **2**. This same pattern of behavior has been observed in the decarboxylation of tertiary acids[5d,e] where a stable carbonium ion is formed.

Decarboxylation of *N*-Nitrosopipecolic Acid. Oxidation of *N*-nitrosopipecolic acid (**5**) with lead(IV) in

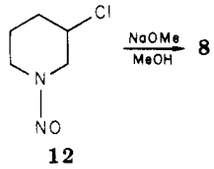


5 8 9 11 10

methylene chloride was greatly enhanced by pyridine and inhibited by oxygen as in the case of nitrosoproline. Unlike the five-membered analogue, oxidation of **5** gave the desired α-acetoxynitrosopiperidine **7** only as a component of a complex mixture. This implies that the carbonium ion formed is not sufficiently stable for exclusive substitution to produce **7**. Due to the flexibility of the six-membered ring, a planar carbonium ion **6** would be difficult to achieve, and therefore solvolysis is not the exclusive reaction. Five major components were isolated from the reaction mixture, 33% of which was **7**.

Decarboxylation experiments with aliphatic acids[5] have shown that isolation of olefinic products is indicative of less stable carbonium ion intermediates. Therefore, decarboxylation of **5** should give *N*-nitroso-1,2,3,4-tetrahydropyridine (**8**) as the major component. The yield of **8** was only 10.6%, but three other products are derived from its interaction with the lead tetraacetate. The three other products have been identified as *N*-nitroso-1,2,3,6-tetrahydropyridine (**9**, 5.7% yield), *N*-nitroso-*cis*-2,3-diacetoxypiperidine (**10**, 22%), and *N*-nitroso-*trans*-2,3-diacetoxypiperidine (**11**, 28%). Products **10** and **11** are derived from the lead tetraacetate oxidation of **8**. A small portion of **8** tautomerizes to the Δ^3 isomer **9**.

N-Nitroso-1,2,3,4-tetrahydropyridine was independently synthesized from *N*-nitroso-3-chloropiperidine (**12**), and

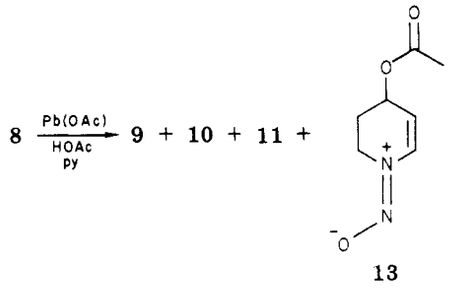


12

1,2,3,6-tetrahydropyridine hydrochloride was converted to the corresponding nitroso compound.[8] These compounds were identified with **8** and **9**, giving unequivocal proof of their structures. To prove that **10** and **11** were derived from the oxidation of **8**, we treated this compound with lead tetraacetate under conditions similar to those used for the oxidative decarboxylation. The reaction mixture was analyzed by GLC/MS; 20% of the mixture was *N*-nitroso-1,2,3,6-tetrahydropyridine (**9**), 1% was *N*-nitroso-*cis*-2,3-diacetoxypiperidine (**10**), and 33% the trans isomer **11**. The major component **13** (45%) was derived from the

Table I. Product Distribution from the Pyridine and the Cu(II)-Catalyzed Oxidative Decarboxylation of *N*-Nitrosopipecolic Acid

conditions	relative product yields, % 7	8	9	10	11	13
1.2 equiv of Pb(IV), 1.2 equiv of py	33.0	10.6	5.7	22	28.0	<1.0
1.2 equiv of Pb(IV), 0.12 equiv of Cu(II)	8.7	17.2	7.8	25	39.7	2.3



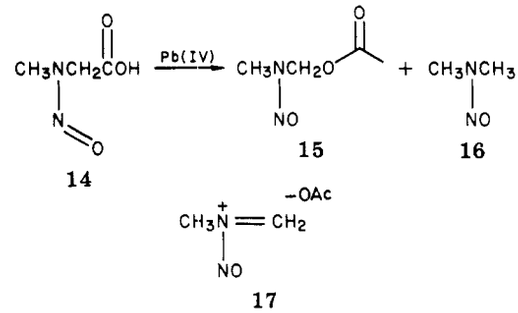
13

allylic oxidation of **8**. Allylic oxidation of olefins with lead tetraacetate is a more favored process[9] than addition of acetate across the double bond. Therefore, formation of **13** was expected. This compound, however, has never been observed during the oxidative decarboxylation of nitrosopipecolic acid in more than 2% yield. This may be explained by the initial breakdown of the lead tetraacetate. The formation of acetoxy radicals probably predominates during oxidative decarboxylation. The oxidation of olefins may involve acetoxy anions, derived from the addition of two electrons to lead tetraacetate.[9] The tautomerization to Δ^3-tetrahydropyridine **9** was unexpected since it has been demonstrated that **8** is the thermodynamic product in the base-catalyzed elimination of *N*-nitroso-3-chloropiperidine (**12**).[7]

Decarboxylation of 5 in the Presence of Cupric Acetate. When cupric acetate is used in combination with lead tetraacetate, the decarboxylations of primary and secondary acids are driven to alkene formation.[5d,e] In the case of nitrosopipecolic acid, the yield of solvolysis product **7** decreases to 8.7%. Olefinic and oxidation products derived from the olefins predominate; relative yields are shown in Table I.

Decarboxylation of *N*-Nitrososarcosine 14. Oxidation of **14** in methylene chloride with lead tetraacetate catalyzed by pyridine gave two major products. The

(7) A far superior method to prepare **8** is by the base-catalyzed epimerization of *N*-nitroso-Δ^3-tetrahydropyridine **9**: R. Kupper and C. Michejda, *J. Org. Chem.*, **44**, 2326 (1979).
(8) W. Lijinsky and H. W. Taylor, *Cancer Res.*, **35**, 3209 (1975).
(9) R. Criegee, *New Methods Prep. Chem.*, **2**, 367 (1963).
(10) Mutagenicity determinations were carried out by A. Wesley Andrews and his staff from the Microbial Mutagenesis screening section, Frederick Cancer Research Center.
(11) W. Lijinsky, L. Keefer, and J. Loo, *Tetrahedron*, **26**, 5137 (1970).
(12) For an independent synthesis and identification of **13**, see J. E. Saavedra, *J. Org. Chem.*, following paper in this issue.



predominant product was (α-acetoxymethylene)methylnitrosamine (**15**, 89.6%). Dimethylnitrosamine (**16**) was also obtained in 7% yield. Although the radical derived from the decarboxylation of **14** was a primary one, the electron delocalization through the nitroso group exerted a stabilizing effect. Therefore, hydrogen radical abstraction was a minor pathway. Hydrogen abstraction is a common reaction when unstable primary radicals are formed.

Warning! The α-acetoxynitrosamines described in this report are potent bacterial mutagens[11] which require no microsomal activation and should be handled with great caution.

Experimental Section

Proton magnetic resonance spectra were measured on a Varian XL-100 spectrometer using $CDCl_3$ as solvent containing 0.5% tetramethylsilane as the internal standard. The IR spectra were obtained on a Perkin-Elmer 467 spectrometer. Mass spectra were taken on a Finnigan 3300 mass spectrometer equipped with a Finnigan 6000 MS data system. Ultraviolet spectra were run as ethanolic or aqueous solutions on a Beckman Acta MVI spectrophotometer. Melting points were determined on an Electrothermal capillary melting point apparatus and were not corrected. Gas chromatographic analyses were carried out on a Shimadzu Model 4BM gas chromatograph equipped with a Hewlett-Packard 18652A A/D converter coupled to the recorder of a flame-ionization detector. An 8 ft, 8% HI-EFF-1BP coated on Gas Chrom Q column was used (Applied Science Laboratories, Inc., State College, PA). The starting materials used were obtained from Aldrich Chemical Co., Milwaukee, WI. Elemental analyses were done at Galbraith Laboratories, Inc., Knoxville, TN.

***N*-Nitrosamino Acids.** The following nitrosamino acids were prepared by the method of Lijinsky et al.:[11] *N*-nitroso-L-proline (**2**), mp 98–100 °C (lit.[11] mp 99–100 °C), $[\alpha]^{25}_D$ −188° (*c* 0.231, EtOH); *N*-nitrosopipecolic acid (**5**), mp 92–94 °C (lit.[11] mp 91–93 °C); *N*-nitrososarcosine (**14**), 66–67 °C (lit.[11] mp 66–67 °C).

Thermal Oxidative Decarboxylations. The solution of the nitrosamino acid (0.5 M) in dichloromethane was placed in a 25-mL two-necked flask equipped with a condenser, a gas-inlet tube, and a rubber septum. Nitrogen or oxygen was introduced into the system with a hypodermic needle through the rubber septum. Lead tetraacetate was added, and the mixture heated to 40 °C. A slow stream of nitrogen was passed over the mixture throughout the course of the reaction. The CO_2 evolved was collected in 10% aqueous potassium hydroxide solution and measured gravimetrically as barium carbonate. In experiments employing pyridine or cupric acetate, it was added before the addition of lead tetraacetate. When the evolution of carbon dioxide had ceased, the reaction mixture was cooled to room temperature and filtered through Celite. The solution was evaporated to near dryness under a stream of nitrogen and the residue extracted with ether. The ether extract was washed with ice-cold 2% hydrochloric acid and then with ice-cold 2% sodium bicarbonate solution, dried over sodium sulfate, and filtered through a layer of magnesium sulfate, and the solvent was removed on a rotary evaporator or under a stream of nitrogen. The crude products were analyzed by gas–liquid chromatography.

α-Acetoxy-*N*-nitrosopyrrolidine (3). To a 0.5 M solution of 1.5 g (10.4 mmol) of *N*-nitroso-L-proline (**2**) in dichloromethane were added 1.2 equiv of pyridine and 5.4 g (12.2 mmol) of lead tetraacetate. The solution was heated to 40 °C for 10 h and worked up as described above. The crude product was purified by column chromatography on silica gel 60 (EM reagents, E. Merck, Darmstadt) in a methylene chloride gradient, giving an optimum yield of 1.5 g (70%) of **3**: bp 98 °C (0.7 mmHg); IR (film) 1745, 1450, 1370, 1235 cm^{-1}; NMR ($CDCl_3$) δ 2.0–2.3 (m, 4 H), 2.09 (s, 3 H), 3.3–3.8 (m, 2 H), 7.4 (m, 1 H); MS *m/z* (rel intensity) 158 (6.9), 99 (23.41), 69 (18.93); UV λ_{max} (H_2O) 350 nm (ε 75), 231 (4834).

Decarboxylation of *N*-Nitrosopipecolic Acid. The reaction conditions used in this experiment gave the optimum yield of α-acetoxynitrosopiperidine **7**. To a 0.5 M solution of 1.2 g (7.6 mmol) of nitrosopipecolic acid in benzene containing 12 mL (15.2 mmol) of pyridine was added 4 g (9.12 mmol) of lead tetraacetate. The mixture was gently refluxed under nitrogen for 3 h. The reaction was worked up, and the products were extracted as described previously. The crude mixture was analyzed by GLC, giving five major components. The compounds were separated on a silica gel column. The first three components required further purification by column chromatography, while the last two were further purified by fractional crystallization.

Peak 1: *N*-nitroso-1,2,3,4-tetrahydropyridine (**8**); GLC yield 10.6%; NMR ($CDCl_3$) δ 1.80 (m, 2 H), 2.20 (m, 2 H), 3.77 (t, 1.2 H, syn), 4.40 (t, 0.8 H, anti), 5.40 (m, 1 H), 7.56 (m, 1 H); MS *m/z* (rel intensity) 112 (71.15), 82 (28.13), 81 (13), 80 (33.80), 67 (11.82), 55 (100).

Peak 2: *N*-nitroso-1,2,3,6-tetrahydropyridine (**9**); GLC yield 5.7%; NMR ($CDCl_3$) δ 2.20 (m, 0.4 H), 2.48 (m, 1.64 H), 3.96 (t, 0.4 H), 4.89 (t, 1.6 H), 4.2 (m, 1.6 H), 4.78 (m, 0.4 H), 5.60–6.04 (m, 2 H); IR (film) 3040, 2920, 1430, 1350, 1330, 1156 cm^{-1}. Compound **9** was prepared by the method of Lijinsky et al.[8] from 1,2,3,6-tetrahydropyridine hydrochloride, bp 44–45 °C (0.2 mmHg), and was identical with peak 2.

Peak 3: α-acetoxy-*N*-nitrosopiperidine (**7**); GLC yield 33%, isolated yield 338 mg (26%); IR (film) 1745, 1456, 1370, 1235 cm^{-1}; NMR ($CDCl_3$) δ 1.83 (br, 4 H), 1.9–2.2 (m, 2 H), 2.04 (s, 0.6 H, syn), 2.1 (s, 2.4 H, anti), 2.7 (sextet, 0.85 H, syn axial), 3.8 (m, 0.15 H, anti axial), 4.84 (q, 1 H), 7.31 (br, 1 H); MS *m/z* (rel intensity) 172 (M^+, 11.12), 142 (1.23), 113 (39.4), 83 (80.6), 55 (78.9), 43 (100); UV λ_{max} (EtOH) 230 nm (ε 4630), 365 (90).

Peak 4: *N*-nitroso-*cis*-2,3-diacetoxypiperidine (**10**); GLC yield 22%. This compound was separated from **11** (see below) by crystallization of the latter. Compound **10** was further purified by filtration through silica gel using methylene chloride as the eluant. This isomer was obtained as an oil: IR (film) 2960, 2925, 2860, 1735, 1460, 1380 cm^{-1}; NMR ($CDCl_3$) δ 1.64 (m, 2 H), 1.9–2.06 (m, 2 H), 2.11 (s, 3 H), 2.18 (s, 3 H), 2.64 (sextet, 1 H), 4.81 (2 br d, 1 H), 5.16 (m, 1 H), 7.47 (d, 0.07 H), 7.63 (d, 0.93 H); MS *m/z* (rel intensity) 230 (M^+, 1.34), 171 (10.51), 141 (9.16), 126 (14.4), 98 (96.5), 82 (7.0), 81 (20.6), 59 (3.3), 43 (100). Anal. Calcd for $C_9H_{14}N_2O_5$: C, 46.95; H, 6.13; N, 12.17. Found: C, 47.12; H, 6.32; N, 12.16.

Peak 5: *N*-nitroso-*trans*-2,3-diacetoxypiperidine (**11**); GLC yield 28%. This compound was further purified after column chromatography by fractional crystallization from light petroleum ether–ether: mp 106–107 °C; IR (KBr) 2990, 2960, 2940, 1740, 1468, 1445, 1317, 1240 cm^{-1}; NMR ($CDCl_3$) δ 1.68 (m, 2 H), 1.98–2.2 (m, 2 H), 2.07 (s, 3 H), 2.12 (s, 3 H), 2.70 (m, 1 H), 4.86 (m, 1 H), 5.20 (q, 2 H), 7.07 (d, 0.07 H, syn), 7.18 (d, 0.93 H, anti, $J_{e,e}$ = 2.5 Hz); MS *m/z* (rel intensity) 230 (M^+, 1.47), 171 (2.52), 141 (1.84), 98 (39.74), 82 (2.99), 81 (8.44), 59 (1.49), 43 (100), 30 (7.27); UV λ_{max} (EtOH) 239 nm (ε 8057), 368 (82). Anal. Calcd for $C_9H_{14}N_2O_5$: C, 46.95; H, 6.13; N, 12.17. Found: C, 46.99; H, 6.38; N, 12.06.

Nuclear Magnetic Resonance Spectra of *N*-Nitroso-*cis*-2,3-diacetoxy- (10) and *N*-Nitroso-*trans*-2,3-diacetoxypiperidine (11). Each of the two isomers **10** and **11** exists with the nitroso group predominantly anti (93%) to the acetoxy group. This is based on the integration of the syn and anti methine protons geminal to the α-acetoxy group. The syn methine of **10** appears as a doublet at δ 7.47, and the anti methine also appears as a doublet at slightly lower field (δ 7.63) with a coupling constant J = 4 Hz, where the equatorial methine is split by a vicinial proton in the axial position. The α-axial proton on the 6-position of **10** gives a sextet centered at δ 2.64; the equatorial proton appears as two broad doublets centered at δ 4.81. The proton geminal

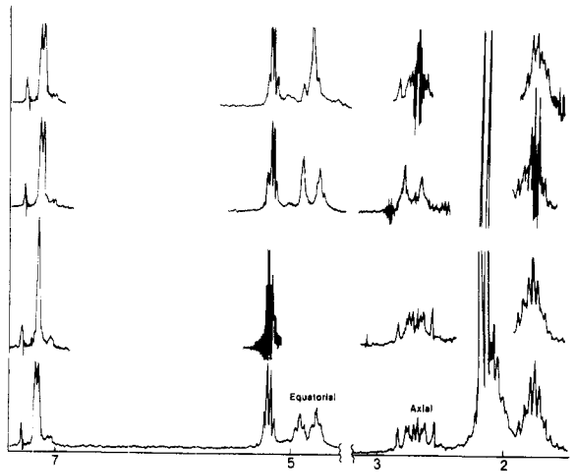


Figure 2. Spin decoupling of *N*-nitroso-*trans*-3,4-diacetoxypiperidine (11).

to the β-acetoxy group gives a multiplet at δ 5.16. The trans isomer 11 gives a similar spectrum; the α-axial proton gives a multiplet centered at δ 2.70 and the equatorial one shows a multiplet between δ 4.8 and 4.94. The syn and anti methine protons appear as doublets at δ 7.06 and 7.18, respectively. The coupling constant between the two methine protons geminal to the acetoxy groups is J = 2.5 Hz. This is a good indication that the two acetoxy groups are axially oriented.

Spin-decoupling experiments with 11 give more conclusive support to the assigned structure (Figure 2). Irradiation of the C-5 methylene protons at δ 1.68 resulted in the collapse of the α-axial mutliplet into two broad signals. The same collapse was observed for the α-equatorial proton. A broad signal at δ 4.86 was observed for the α-equatorial proton on irradiation of the geminal axial proton at δ 2.70. The α-methine proton at δ 7.18 became a singlet upon irradiation of the methine proton on C-3 at δ 5.2. This is a clear indication that the two acetoxy groups are vicinal.

***N*-Nitroso-3-chloropiperidine (12).** Thirteen grams (0.084 mol) of 3-hydroxypiperidine partially dissolved in 100 mL of methylene chloride was cooled to −5 °C. Thionyl chloride (15.4 mL, 0.11 mol) was added dropwise, the ice bath removed, and the solution stirred at room temperature overnight. The solvent was removed on a rotary evaporator. The last traces of thionyl chloride were removed under high vacuum (0.2 mmHg). The residual oil was cooled to 5 °C, and ice–water was added until the residue had dissolved. A solution of 13.2 g (0.2 mol) of sodium nitrite in 100 mL of water was added dropwise. Once addition was complete, the ice bath was removed and the mixture stirred for 1 h at 25 °C. The mixture was extracted with dichloromethane and the organic layer washed with 5% sodium bicarbonate solution, dried over anhydrous potassium carbonate, and filtered through a pad of magnesium sulfate. Evaporation of the solvent under vacuum gave 6.9 g of a brown oil. The crude product was analyzed by GLC at 165 °C, with a helium flow rate of 60 mL/min, and it contained 70% of *N*-nitroso-3-chloropiperidine. The crude mixture was filtered through a silica gel column eluted with dichloromethane. The purity of each fraction was determined by GLC. A yield of 3.15 g (22.6%) of 1 was obtained: UV λ_{max} (EtOH) 355 nm (ε 85.3); MS m/z (rel intensity) 148 (100), 118 (31.2), 82 (60.3); isotope cluster 148 (M^+, 100), 149 (M + 1, 11.76), 150 (M + 2, 33.3%). Anal. Calcd for $C_5H_9N_2OCl$: C, 40.41; H, 6.11; N, 18.85; Cl, 23.86. Found: C, 40.61; H, 6.11; N, 19.05; Cl, 24.01.

Preparation of an Authentic Sample of *N*-Nitroso-1,2,3,4-tetrahydropyridine (8).[7] A 0.5 M solution of 208 mg (1.4 mmol) of *N*-nitroso-3-chloropiperidine (12) in dry methanol was added to 151 mg (2.8 mmol) of sodium methoxide. The mixture was stirred at room temperature for 7 h and then evaporated to near dryness under a stream of nitrogen, and the residue was extracted with methylene chloride. The solution was washed with water and dried over potassium carbonate, and the solvent was removed under nitrogen. When the residue was vacuum distilled, it gave 118 mg (75%) of 8. Gas chromatographic analysis of the product indicated that no Δ^3 isomer 9 was present: bp 42 °C (0.4 mmHg); IR (film) 3090, 2940, 1650, 1440, 1300 cm^{-1}. UV λ_{max} (H_2O) 281 nm (ε 8467), 206 (4433). Anal. Calcd for $C_5H_8N_2O$: C, 53.56; H, 7.19; N, 24.98. Found: C, 53.44; H, 7.36; N, 25.08.

Oxidation of 8 with Lead Tetraacetate. To a solution of 34 mg (0.3 mmol) of 8 in 0.6 mL of methylene chloride were added 0.05 mL of glacial acetic acid, 0.5 mL of anhydrous pyridine, and 160 mg (0.36 mmol) of lead tetraacetate. The reaction mixture was stirred at 35 °C overnight and then diluted with 10 mL of ether. The mixture was worked up as described for the thermal oxidative decarboxylations and gave 22 mg of a yellow oil. Gas chromatographic analysis of the crude mixture at 165 °C gave the following relative distribution of products: 9 (20%), 13 (45%), 10 (1%), 11 (33%). The structural assignment of the products was verified by GLC/MS: *N*-nitroso-4-acetoxy-1,2,3,4-tetrahydropyridine (13), MS m/z (rel intensity) M + 70 (0.07), 155 (0.8), 111 (0.07), 81 (30), 80 (28), 59 (11.3), 43 (100). This compound was separated from the other components by column chromatography and was identical with an authentic sample of *N*-nitroso-4-acetoxy-1,2,3,4-tetrahydropyridine.[12]

***N*-(α-Acetoxymethylene)-*N*-methylnitrosamine (15).** To a 0.5 M solution of 821 mg (6.95 mmol) of nitrososarcosine in methylene chloride was added 0.8 mL (10 mmol) of pyridine. Lead tetraacetate (3.7 g, 8.34 mmol) was added to the solution, and the resulting mixture was refluxed under nitrogen for 3 h. The reaction mixture was worked up as described above. GLC analyses of the crude product before distillation indicated that 7.1% of the mixture was nitrosodimethylamine. Compound 15 was obtained in 37% yield (335 mg): bp 94–95 °C (15 mmHg) [lit.[1a] bp 113 °C (32 mmHg), 36 °C (9.5 mmHg)]; IR (film) 1750, 1470, 1410 cm^{-1}; NMR ($CDCl_3$) δ 2.12 (s, 3 H), 3.05 (s, 3 H), 6.14 (s, 2 H); MS m/z (rel intensity) M + 132 (2.6), 102 (2.5), 73 (100), 43 (41.18), 42 (51.24), 41 (6).

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