Aralkylation of Potassium Ethylnitrosolate. Ring Closure of Nitrosolic Acid Esters

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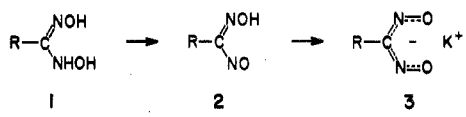
The aralkylation of potassium ethylnitrosolate has been examined as a synthetic route to nitrosolic acid esters. The reaction of potassium ethylnitrosolate with representative benzylic halides did not stop at the ester stage but resulted in the formation of heterocyclic *N*-oxides derived from the 1,2,4-oxadiazole ring system. The product was shown to be the N-4 rather than the N-2 oxide on the basis of NMR studies. A formal mechanism is proposed involving intramolecular reaction of the nitroso group of an intermediate nitrosolic acid ester with the benzylic methylene, followed by oxidation to the observed product. The sequence provides a new route to unsymmetrically substituted 1,2,4-oxadiazole 4-oxides. When the benzylic methylene is further substituted, as in the case of triphenylmethyl chloride, reaction with potassium ethylnitrosolate terminates at the corresponding ester.

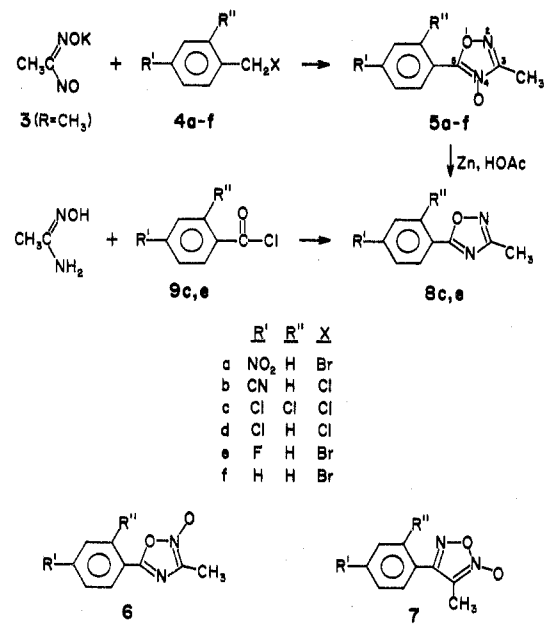
Nitrosolic acids (**2**) constitute a rather obscure class of functionality even though the first examples were reported by Wieland[1] in the early 1900's. They have been prepared from oxyamide oximes (**1**) by disproportionation[1] or, more recently, by periodate oxidation.[2] Although the acids themselves are not sufficiently stable to permit facile isolation, the metal salts (**3**) of the acid are easily prepared and are sufficiently stable to be isolated. The chemical properties and reactivity of the nitrosolic acid salts have not been studied, although electrochemical reactions have been investigated and the pK_a's of a series of acids have been determined.[3] We were interested in the potential reactivity of the nitrosolic acid esters, a class of compounds not heretofore prepared. Of the routes considered for the synthesis of the desired esters, oxidation of an *O*-alkyl oxyamide oxime or O-alkylation of a nitrosolate salt appeared the most straightforward, and we chose to examine the latter route. Alkylation of oxime anions is known to result in N- or O-alkylation, and O-alkylation can be favored through selection of appropriate reaction conditions.[4] C-Alkylation is theoretically possible but has not been detected. The possibility of C-alkylation in nitrosolates might be greater than for their oxime analogues because of the second electron-withdrawing group.[5] Therefore, C-alkylation had to be considered as an additional possibility. We report here the reaction of potassium ethylnitrosolate (**3**, R = CH_3) with several aralkyl halides and the preparation of the trityl ester.



1 **2** **3**

Results and Discussion

Potassium ethylnitrosolate (**3**, R = CH_3) is a blue, crystalline solid which can be stored at 0 °C for several weeks without decomposition. When *p*-nitrobenzyl bromide and potassium ethylnitrosolate were allowed to react in acetone, the acid salt was rapidly consumed. A yellow, crystalline compound was isolated from the reaction mixture, but it quickly became apparent to us that this was not the desired *p*-nitrobenzyl ester. The mass spectrum of the compound gave a molecular ion at *m/e* 221 instead of 223 as expected. The NMR spectrum showed only an A_2B_2 pattern in the aromatic region and a three-hydrogen signal for a methyl group (δ 2.80); there was no signal for benzylic protons. Analytical data were consistent with the formula $C_9H_7N_3O_4$ but not with the expected formula $C_9H_9N_3O_4$. One structure compatible with these data is that of 3-methyl-5-(4-nitrophenyl)-1,2,4-oxadiazole 4-oxide (**5a**). The isomeric 1,2,4-oxadiazole 2-oxide (**6**) was also a plausible structure, but appeared less likely, and so far as we could determine no N-2 oxides of this ring system have been reported. The isomeric furazan (**7**) was unlikely on the basis of mass spectral evidence.[6] Reduction of the product to the known 3-methyl-5-(4-nitrophenyl)-1,2,4-oxadiazole would serve to confirm the heterocyclic ring structure. However, the sensitivity of the nitro group to reduction would make this a difficult transformation. Therefore, we prepared the 2,4-dichlorophenyl analogue (**5c**) by the reaction of α,2,4-trichlorotoluene with potassium ethylnitrosolate. Treatment of this *N*-oxide with Zn/HOAc[7] resulted in the formation of 5-(2,4-dichlorophenyl)-3-methyl-1,2,4-oxadiazole (**8c**) identical



with an authentic sample (melting point, TLC, and NMR) prepared from **9c** by the method of Tieman and Kruger.[8] This confirmed the structure of the heterocyclic ring, the presence of an *N*-oxide, and limited the possible structures to **5** and **6**.

The position of the *N*-oxide function was identified through a comparison of the NMR spectra of compound **8c** and its *N*-oxide precursor. The resonance of the 6-H in the 2,4-dichlorophenyl ring could be assigned in both compounds from the values of the coupling constants.[9] In **8c** the 6-H appears at δ 8.10, while in the *N*-oxide this hydrogen is found at δ 9.10; i.e., there is a downfield shift of 1.00 ppm in the *N*-oxide. A shift of this magnitude cannot be due to inductive effects in view of the small change in the chemical shifts of the 3- and 5-H's (~0.03 ppm further downfield in the *N*-oxide) and in

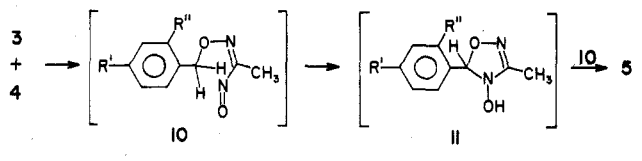
the methyl protons (~0.05 ppm further downfield in the *N*-oxide). The strong deshielding effect must be due to anisotropy of the *N*-oxide[10] or to van der Waals deshielding[11] rather than inductive effects. Models clearly indicate that the preferred conformations of the N-2 oxide place the *N*-oxide oxygen at a relatively large distance from the 6-H. The N-4 oxide however, would have strong steric interaction with the 2-Cl, restricting the system to conformations where the two rings are not coplanar, or where coplanarity of the rings forces the *N*-oxide very close to the 6-H. The large change in the chemical shift of the 6-H in the *N*-oxide relative to the parent heterocyclic ring system (**8c**) is very good evidence for proximity of the 6-H and the *N*-oxide function, and thus forms the basis for the assignment of structure **5** to the *N*-oxides isolated from the reaction **3** + **4a–f.**

Further support for this assignment as the N-4 oxide was found with the *p*-fluorophenyl analogue **5e** prepared from the reaction of *p*-fluorobenzyl bromide with potassium ethylnitrosolate. The proton resonances of this compound could be assigned on the basis of J_{FH} values.[12] The protons ortho to fluorine appear at δ 7.43 as a pseudotriplet (J_{FH} = 9, J_{HH} = 9 Hz) while the protons meta to the fluorine appear at δ 8.68 as a quartet (J_{FH} = 5, J_{HH} = 9 Hz).[12b] Reduction of the *N*-oxide with Zn/HOAc afforded 5-(*p*-fluorophenyl)-3-methyl-1,2,4-oxadiazole (**8e**), identical with an authentic sample (melting point, TLC, and NMR) prepared according to the method of Tieman and Krüger.[8,13] The phenyl protons were again assigned on the basis of their J_{FH} values (3-, 5-H's at 7.37, J_{FH} = 9, J_{HH} = 9 Hz; 2-, 6-H's at 8.17, J_{FH} = 6, J_{HH} = 9 Hz). In this pair, there is a downfield shift of 0.51 ppm for the 2 and 6 protons of the *N*-oxide (**5e**) relative to the reduced form (**8e**). Although this is a smaller $\Delta\delta$ than found for the 2,4-dichlorophenyl compounds, a shift of this magnitude would be predicted if the deshielding effect of the *N*-oxide were averaged over both ortho protons in the absence of a bulky group at the 2 position. Accordingly, on the basis of the NMR data for both sets of compounds, the products of the general reaction, **3** + **4**, are clearly of structure **5.**

The condensation of *O*-acyl amidoximes[8] provides an easy entry to the 1,2,4-oxadiazole system and numerous examples of substituted oxadiazoles have been reported.[13] A literature survey revealed that N-4 oxides of this system have also been prepared[14] although apparently not via direct oxidation of the parent oxadiazole.[15] The reported 1,2,4-oxadiazole 4-oxides were obtained from the dimerization of nitrile oxides. Because furazans are frequently the major product of nitrile oxide dimerization[16] and because dimerization provides only heterocycles with identical substituents in the 3 and 5 positions, this new route to substituted 1,2,4-oxadiazole 4-oxides is of supplementary interest. We have examined this reaction with additional substituted benzylic halides (**4a–f**) to illustrate generality. With benzylic halides bearing strong electron-withdrawing groups, e.g., nitro or cyano, the reaction proceeds in good yield at room temperature in acetone, while reactions with benzylic halides bearing less strongly electron-withdrawing groups, e.g. Cl, F (or H), required higher temperatures or a more polar solvent.

The following reaction sequence can account for the formation of oxadiazole 4-oxides in this reaction (Scheme I). Under the conditions which we employed, O-alkylation would be expected, resulting in a benzylic ester (**10**) of nitrosolic acid. The free nitroso group of this ester presumably reacts with the benzylic methylene to produce the intermediate hydroxylamine **11**, which is then oxidized by a second mole of ester to afford the observed product. The alternative dehydration of **11** to an oxadiazole and subsequent oxidation was ruled out when it was determined that authentic samples of oxadiazoles were not oxidized under these conditions by the nitrosolic acid salt.

Scheme I



The actual oxidant involved in this reaction may be a second mole of the nitrosolic acid ester (**10**), for in experiments in which 2 mol of potassium ethylnitrosolate was added per mole of halide, 1 molar equiv of the salt was recovered unchanged. Our presumptive evidence for the presence of reduction products of **10** was supported by mass spectral data. Substitution of an alternative oxidant would be attractive because it would reduce the ratio of 2 equiv of starting material per equivalent of product to a one-to-one ratio and would not be destructive of the less accessible starting material. However, attempts to employ air, nitrosobenzene, or potassium periodate as the alternative oxidant did not result in increased yield.

There are several precedents for the proposed reaction scheme. The intermolecular reaction of an aromatic nitroso compound with an active methylene is known to afford either a nitrone, an imine, or a mixture.[17] Precedent for the proposed intramolecular condensation (**10** → **11**) is found in the reaction of benzylic halides with aromatic nitroso compounds to afford nitrones, presumed to arise via condensation to an hydroxylamine and loss of HX.[18] The isolation of 1,3-dimethylalloxazine 10-oxide upon attempted nitrosation of 1,3-dimethyl-6-anilinouracil is analogous to the oxidation of **11**, and in this case it was suggested that excess nitrous acid served as an oxidant of an intermediate hydroxylamine.[19]

The isolation of these 1,2,4-oxadiazole 4-oxides indicates that C-alkylation is not a significant process under the stated reaction conditions. The possibility of an N-alkylated intermediate resulting in the oxadiazole 4-oxide appears remote, unless there is a facile rearrangement to the *O*-aralkyl ester[20] or unless such an N-alkylated intermediate serves only as an oxidant.

In order to take advantage of the foregoing knowledge for the preparation of an isolable nitrosolic acid ester, we ran the reaction of triphenylmethyl chloride with potassium ethylnitrosolate. A green crystalline solid was obtained in ca. 60% yield following purification by chromatography on silica gel. The assignment of the structure as $CH_3(ON)C{=}NOCPh_3$ (**12**) was supported by infrared and mass spectral data, including a $(C_6H_5)_3COH^+$ ion even in the field desorption spectrum.[21] The ester is stable at 0 °C but appears to undergo slow decomposition at room temperature.

Our experiments provide sufficient encouragement for continued investigation of nitrosolic acid derivatives.

Experimental Section

Melting points were recorded on a Büchi melting point apparatus and are uncorrected. The NMR spectra were recorded on a Varian Associates A-60 or HA-100 spectrometer using tetramethylsilane as an internal standard. The ultraviolet spectra were obtained on a Beckman Acta MVI spectrophotometer, and the infrared spectra were obtained on a Perkin-Elmer Model 337 infrared spectrophotometer. Microanalyses were performed by Mr. Josef Nemeth and associates, who also weighed samples for the quantitative electronic absorption spectra. Low-resolution mass spectra were obtained by Mr. J. Wrona on a Varian-MAT CH-5 spectrometer coupled with a 620i computer and STATOS recorder.

Potassium Ethylnitrosolate (3, R = CH_3). Potassium ethylnitrosolate was prepared through the following sequence. Acetamidoxime was prepared by the condensation of hydroxylamine[22] and acetonitrile according to the procedure of Lenaers et al.,[23] mp 133–134

°C (lit.[23] 135 °C). The acetamidoxime was treated with hydroxylamine hydrochloride according to the procedure of Armand[24] to afford acetoxyamidoxime (1, R = CH_3), which was isolated as its hydrochloride salt, mp 154–155 °C (lit.[24] 156 °C). Potassium ethylnitrosolate was prepared by periodate oxidation of acetoxyamidoxime according to the procedure of Armand.[2] After acidification to pH 6 with saturated sodium dihydrogen phosphate solution, the nitrosolic acid was extracted with ether, and the combined ether extracts were dried (Na_2SO_4) and then treated with a solution of 1 equiv of potassium *tert*-butoxide in methanol. Careful scratching[25] resulted in the formation of a blue, crystalline solid which was then collected by filtration, mp 205 °C dec (lit.[1] 207 °C dec).

3-Methyl-5-(*p*-nitrophenyl)-1,2,4-oxadiazole 4-Oxide (5a). *p*-Nitrobenzyl bromide (432 mg, 2 mmol) was added to a suspension of potassium ethylnitrosolate (252 mg, 2 mmol) in acetone (30 ml). The blue color quickly disappeared (≈10 min), resulting in a yellow solution and a white precipitate. The reaction mixture was stirred overnight under nitrogen at 20 °C. Filtration and evaporation of the filtrate to dryness resulted in a yellow solid. Crystallization from acetone afforded 139 mg of fine yellow needles. Further concentration of the mother liquor resulted in a second crop (60 mg) bringing the total yield to 92% (based on *p*-nitrobenzyl bromide and assuming consumption of 2 mol of the nitrosolic ester per mole of product): mp 177–178 °C; λ_{max} (EtOH) ($\epsilon \times 10^{-3}$) 347 (8.88), 254 (11.8); NMR [$(CD_3)_2CO$] δ 2.50 (s, 3, CH_3), 8.49 (d, 2, J = 9 Hz, 3-, 5-H's), 8.85 (d, 2, J = 9 Hz, 2-, 6-H's); mass spectrum (70 eV) *m/e* (rel intensity) 221 (52, M^+), 205 (10, $M^+ - O$), 150 (100, $O_2NC_6H_4CO^+$).

Anal. Calcd for $C_9H_7N_3O_4$: C, 48.87; H, 3.19; N, 19.00. Found: C, 49.20; H, 3.34; N, 19.30.

5-(4-Cyanophenyl)-3-methyl-1,2,4-oxadiazole 4-Oxide (5b). α-Bromo-*p*-tolunitrile (392 mg, 2.0 mmol) was added to a suspension of potassium ethylnitrosolate (252 mg, 2.0 mmol) in acetone and the mixture was stirred overnight at room temperature. The mixture was then filtered and the filtrate was concentrated in vacuo to a thin oil. Addition of ether and filtration gave **5b** (151 mg, 75%) as a white solid, recrystallized from acetone as colorless needles: mp 172–173 °C; λ_{max} (EtOH) ($\epsilon \times 10^{-3}$), 332 (10.8), 250 (14.5); NMR [$(CD_3)_2CO$] δ 2.50 (s, 3, CH_3), 8.06 (d, 2, J = 8 Hz, 3-, 5-H's), 8.76 (d, 2, J = 8 Hz, 2-, 6-H's); mass spectrum (70 eV) *m/e* (rel intensity) 201 (4, M^+), 130 (100, $NCC_6H_4CO^+$).

Anal. Calcd for $C_{10}H_7N_3O_2$: C, 59.70; H, 3.51; N, 20.89. Found: C, 59.81; H, 3.71; N, 20.86.

5-(2,4-Dichlorophenyl)-3-methyl-1,2,4-oxadiazole 4-Oxide (5c). α,2,4-Trichlorotoluene (391 mg, 2.0 mmol) was added to a suspension of potassium ethylnitrosolate (252 mg, 2.0 mmol) in acetone (25 ml) and the resulting mixture was heated at reflux for ~1.5 h. The mixture was then filtered to remove KCl and the filtrate was evaporated to dryness in vacuo. The residue was purified by column chromatography on silica gel (5% acetone/$CHCl_3$) to afford 193 mg (79%) of **5c** as colorless crystals, recrystallized from acetone: mp 146–147 °C; λ_{max} (EtOH) ($\epsilon \times 10^{-3}$) 315 (7.74), 240 (10.0); NMR [$(CD_3)_2CO$] δ 2.49 (s, 3, CH_3), 7.65 (dd, 1, J = 2.2, 8.8 Hz, 5-H), 7.78 (dd, 1, J = 0.5, 2.2 Hz, 3-H), 9.10 (dd, 1, J = 0.5, 8.8 Hz, 6-H); mass spectrum (70 eV) *m/e* (rel intensity), 248 (3, M^+), 246 (17, M^+), 244 (26, M^+) 177 (12, $Cl_2C_6H_3CO^+$), 175 (67, $Cl_2C_6H_3CO^+$), 173 (100, $Cl_2C_6H_3CO^+$).

Anal. Calcd for $C_9H_6Cl_2N_2O_2$: C, 44.11; H, 2.47; N, 11.43. Found: C, 43.95; H, 2.55; N, 11.31.

5-(2,4-Dichlorophenyl)-3-methyl-1,2,4-oxadiazole (8c). Method A. A sample prepared from 2,4-dichlorobenzoyl chloride and acetamidoxime according to the general procedure of Tieman[8,13] was crystallized from ethanol: yield, 79%; mp 79–80 °C; NMR [$(CD_3)_2CO$] δ 2.43 (s, 3, CH_3), 7.61 (dd, J = 2.0, 8.4 Hz, 5-H), 7.74 (dd, 1, J = 0.4, 2.0 Hz, 3-H), 8.10 (dd, 1, J = 0.4, 8.4 Hz, 6-H); mass spectrum (70 eV) *m/e* (rel intensity) 232 (8, M^+), 230 (44, M^+), 228 (69, M^+), 175 (17, $Cl_2C_6H_3CN^+$), 173 (74, $Cl_2C_6H_3CN^+$), 171 (100, $Cl_2C_6H_3CN^+$).

Anal. Calcd for $C_9H_6Cl_2N_2O$: C, 47.19; H, 2.64; N, 12.22. Found: C, 46.99; H, 2.82; N, 12.09.

Method B. Zinc dust was added to a solution of **5c** (12 mg, 0.05 mmol) in acetic acid (2 ml) and the mixture was stirred at room temperature for 1 h, then heated at reflux for 30 min. The mixture was filtered and the filtrate was evaporated in vacuo to give 12 mg (~100%) of **8c**, identical with the material from method A by melting point, TLC, and NMR.

5-(4-Chlorophenyl)-3-methyl-1,2,4-oxadiazole 4-Oxide (5d). α,*p*-Dichlorotoluene (322 mg, 2.0 mmol) was added to a suspension of potassium ethylnitrosolate (252 mg, 2.0 mmol) in acetone and the resulting mixture was heated at reflux for 16 h. Workup in the usual manner and column chromatography gave **5d** (185 mg, 88%) as a white, crystalline solid: mp 145–146 °C; λ_{max} (EtOH) ($\epsilon \times 10^{-3}$), 317 (11.9), 242 (12.5), 228 (sh, 6.96); NMR [$(CD_3)_2CO$] δ 2.46 (s, 3, CH_3), 7.67 (d, 2, J = 9 Hz, 3-, 5-H's), 8.58 (d, 2, J = 9 Hz, 2-, 6-H's); mass spectrum (70 eV) *m/e* (rel intensity), 212 (8, M^+), 210 (23, M^+), 141 (33, $ClC_6H_4CO^+$), 139 (100, $ClC_6H_4CO^+$).

Anal. Calcd for $C_9H_7ClN_2O_2$: C, 51.32; H, 3.35; N, 13.30. Found: C, 51.44; H, 3.48; N, 13.13.

5-(4-Fluorophenyl)-3-methyl-1,2,4-oxadiazole 4-Oxide (5e). 4-Fluorobenzyl bromide[26] (1.34 g, 7.1 mmol) was added to a suspension of potassium ethylnitrosolate (0.89 g, 7.1 mmol) in methanol. The reaction mixture was stirred at room temperature for ~16 h, filtered to remove KBr, and evaporated to dryness in vacuo. The residue was purified by column chromatography on silica gel (5% acetone/$CHCl_3$) to afford **5e** (544 mg, 79%), recrystallized from ethanol: mp 138–139 °C; λ_{max} (EtOH) ($\epsilon \times 10^{-3}$) 310 (9.87), 243 (9.52), 226 (sh, 7.62); NMR [$(CD_3)_2CO$] δ 2.46 (s, 3, CH_3), 7.42 (dd, 2, J = 9, 9 Hz, 3-, 5-H's), 8.68 (dd, 2, J = 5, 9 Hz, 2-, 6-H's); mass spectrum (70 eV) *m/e* (rel intensity) 194 (18, M^+), 123 (100, $FC_6H_4CO^+$).

Anal. Calcd for $C_9H_7FN_2O_2$: C, 55.67; H, 3.63; N, 14.43. Found: C, 55.38; H, 3.58; N, 14.50.

5-(*p*-Fluorophenyl)-3-methyl-1,2,4-oxadiazole (8e). Method A. A sample was prepared from *p*-fluorobenzoyl chloride and acetamidoxime according to the general procedure of Tieman[8,13] and purified by column chromatography on silica gel ($CHCl_3$ eluent): yield 62%; mp 80–81 °C; NMR [$(CD_3)_2CO$] δ 2.38 (s, 3, CH_3), 7.37 (t, 2, J = 9, 9 Hz, 3-, 5-H's), 8.17 (dd, 2, J = 6, 9 Hz, 2-, 6-H's); mass spectrum (70 eV) *m/e* (rel intensity) 178 (87, M^+), 121 (100, $FC_6H_4CN^+$).

Anal. Calcd for $C_9H_7FN_2O$: C, 60.67; H, 3.96; N, 15.72. Found: C, 60.53; H, 4.01; N, 15.76.

Method B. Zinc dust was added to a solution of **5e** (15 mg, 0.08 mmol) in acetic acid (2 ml) and the mixture was heated at reflux for 30 min. Analysis by TLC indicated that complete reduction had occurred. The reaction mixture was filtered and the filtrate was evaporated to dryness in vacuo to afford **8e** (14 mg, ~100%). This material was identical with that obtained from method A by melting point, TLC, and NMR.

3-Methyl-5-phenyl-1,2,4-oxadiazole 4-Oxide (5f). Benzyl bromide (342 mg, 2.0 mmol) was added to a suspension of potassium ethylnitrosolate (252 mg, 2.0 mmol) in methanol and the resulting mixture was stirred at room temperature for 1 h. Workup in the usual manner and purification by column chromatography gave 132 mg (75%) of **5f** as a white solid, recrystallized from ethanol: mp 120–121°; λ_{max} (EtOH) ($\epsilon \times 10^{-3}$) 311 (8.64), 243 (8.90), 220 (sh, 6.89); NMR [$(CD_3)_2CO$] δ 2.46 (s, 3, CH_3), 7.58–7.74 (m, 3, 3-, 4-, and 5-H's), 8.52–8.64 (m, 2, 2-, 6-H's); mass spectrum (70 eV) *m/e* (rel intensity) 176 (7, M^+), 105 (85, $C_6H_5CO^+$), 77 (100, $C_6H_5^+$).

Anal. Calcd for $C_9H_8N_2O_2$: C, 61.36; H, 4.58; N, 15.90. Found: C, 61.49; H, 4.68; N, 16.09.

Triphenylmethyl Ethylnitrosolate (12). Triphenylmethyl chloride (279 mg, 1.0 mmol) was added to a suspension of potassium ethylnitrosolate (126 mg, 1.0 mmol) in acetone and the resulting mixture was stirred at room temperature for 30 min. The mixture was filtered and the filtrate was evaporated to dryness in vacuo. The residue was purified by column chromatography on silica gel ($CHCl_3$ eluent) to afford 176 mg (61%) of **12** as a green, crystalline solid: mp 108–112 °C dec; ir 1500 cm^{-1}; NMR (CCl_4) δ 1.58 (s, 3, CH_3), 7.10–7.50 [m, 15, $(C_6H_5)_3C$–]; field desorption mass spectrum *m/e* 260 [$(C_6H_5)_3COH^+$], 243 [$(C_6H_5)_3C^+$].

Anal. Calcd for $C_{21}H_{18}N_2O_2$: C, 76.34; H, 5.49; N, 8.48. Found: C, 76.58; H, 5.34; N, 7.38.

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Registry No.—**3** (R = CH_3), 59562-60-6; **4a**, 100-11-8; **4b**, 17201-43-3; **4c**, 94-99-5; **4d**, 104-83-6; **4e**, 459-46-1; **4f**, 100-39-0; **5a**, 59562-61-7; **5b**, 59562-62-8; **5c**, 59562-63-9; **5d**, 59562-64-0; **5e**, 59562-65-1; **5f**, 59562-66-2; **8c**, 59562-67-3; **8e**, 59562-68-4; **12**, 59562-69-5; triphenylmethyl chloride, 76-83-5.

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(25) Salts of nitrosolic acids explode at their melting points. Ethylnitrosolic acid salts are not known to be shock sensitive, but due caution is advised.
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A New Synthetic Approach to the 3-Benzazepine Skeleton through Pinacol–Pinacolone Rearrangement

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Treatment of 2′-(β-*N*-benzyloxycarbonyl-*N*-methyl)aminoethyl-3,4,4′,5′-tetramethoxystilbene oxide (**13**), prepared from laudanosine (**9**) via 2′-(β-*N*-benzyloxycarbonyl-*N*-methyl)aminoethyl-3,4,4′,5′-tetramethoxystilbene (**11**), with methanolic potassium hydroxide gave the diol **1**, and the epoxide **13** and diol **1** were treated with acetic acid in the presence of *p*-toluenesulfonic acid to afford 2,3-dihydro-7,8-dimethoxy-5-(3,4-dimethoxyphenyl)-3-methyl-1*H*-3-benzazepine (**17**). 2,3-Dihydro-3-methyl-7,8-methylenedioxy-5-(3,4-methylenedioxyphenyl)-1*H*-3-benzazepine (**18**) was also obtained from 2-methyl-6,7-methylenedioxy-1-(3,4-methylenedioxybenzyl)isoquinoline through stilbene **12**, epoxide **14**, and diol **2**.

The 3-benzazepine skeleton is observed in the rhoeadine, isopavine, and cephalotaxine alkaloids[1,2] and is found to be an important intermediate for the total syntheses of these alkaloids. Several synthetic methods for the 3-benzazepine skeleton have been applied to the total synthesis of alkaloids.[3] We have now investigated application of the pinacol rearrangement and related epoxide reactions[4,5] for the synthesis of these benzazepine alkaloids. Three types of products appeared possible from pinacol rearrangement of unsymmetrical stilbene diol as shown in Scheme I.[6]

Laudanosine (**9**) was treated with benzyloxycarbonyl chloride in the presence of aqueous sodium hydroxide to give the stilbene **11**, which indicated a *trans*-stilbene chromophore at 330 nm[7] in the uv spectrum (MeOH) and a urethane system at 1680 cm^{-1} in the ir spectrum ($CHCl_3$). Oxidation of the stilbene **11** with *m*-chloroperbenzoic acid proceeded smoothly to afford the epoxide **13**, which on treatment with methanolic potassium hydroxide solution yielded the dihydroxyurethane **1**. The NMR spectrum ($CDCl_3$) revealed the presence of two protons attached to hydroxyl and phenyl groups (δ 4.75 as broad singlet) and the ir spectrum showed hydroxyl and urethane groups at 3400 and 1680 cm^{-1}, respectively. The compound **1** was treated with acetone in the presence of perchloric acid to give the acetonide **15**, whose ir spectrum showed urethane at 1680 cm^{-1}, and the NMR spectrum revealed the presence of two methyl groups due to an acetonide (δ 1.70 as singlet), which suggested that two phenyl groups were located trans to each other because of the same chemical shift of two methyl groups on an acetonide. The compound **2** was obtained by the same way as described for the compound **1** from benzylisoquinoline **10** through the stilbene **12** and the epoxide **14**. The diol **2** was also converted into the acetonide **16**.

Compounds **1** and **13** were, independently, treated with acetic acid in the presence of *p*-toluenesulfonic acid to afford the same compound **17** in 46 and 25.3% yield, respectively, whose NMR spectrum showed the presence of an *N*-methyl group (δ 2.90). The uv spectrum showed λ_{max} 306 nm which shifted to 298 nm on addition of concentrated hydrochloric acid. This shift indicated the presence of a conjugated enamine system. All spectral data of the product **17** were identical with those of an authentic sample.[8] The diol **2** was also treated under the same condition as described above to give the compound **18** in 11.6% yield.

Experimental Section

Melting points are uncorrected. NMR spectra were measured with a JNM-PMX-60 spectrometer (tetramethylsilane as an internal reference), ir spectra with a Hitachi 215 spectrophotometer, uv spectra with a Hitachi 124 spectrophotometer, and mass spectra with a Hitachi RMU-7 spectrometer.

2′-(β-*N*-Benzyloxycarbonyl-*N*-methyl)aminoethyl-3,4,4′,5′-tetramethoxystilbene (11). To a stirred solution of laudanosine (**9**, 25 g) in methylene chloride (200 ml) were added in portions a solution of benzyloxycarbonyl chloride (13.2 g) in methylene chloride (200 ml) and a solution of sodium hydroxide (3.4 g) in water (100 ml) separately within 1 h at room temperature. After the stirring had been continued for 1 h at room temperature, the organic layer was separated and the aqueous layer was extracted with methylene chloride. The combined organic layers were washed with water, dried over Na_2SO_4, and evaporated to leave an orange, viscous oil, which was triturated with ethanol to give the stilbene **11** (25.9 g, 75.3%) as colorless prisms: mp 126–127 °C; uv (MeOH) 295 and 330 nm; ir ($CHCl_3$) 1680 cm^{-1}