Preparative chromatography of the mixture in system F afforded 3.65 mg (47%) of pure **20** (R_f 0.72, system A).

Reaction of 18 with Ethyl Chloroformate. Compound **18** (5.98 mg, 0.0132 mmol) dissolved in tetrahydrofuran (5 mL) was treated with triethylamine (6.10 µL, 0.0436 mmol) and ethyl chloroformate (3.80 µL, 0.0396 mmol) at 52 °C (3 h). The reaction mixture was then evaporated to dryness in vacuo. Thin-layer analysis in system A of the violet residue indicated the presence of two compounds, R_f 0.72 and 0.66. Preparative thick-layer chromatography in system E afforded 3.38 mg (49%) of **21** (R_f 0.72, system A): mp 84–87 °C; IR (CHCl$_3$) 3510, 3370, 3020, 1735, 1715, 1615, 1575, 1505, 1390, 1355, 1270, 1210, 1175, 1155, 1090 cm^{-1}; UV (MeOH) λ_{max} nm 205, 255, 308, 345; field-desorption mass spectrum, m/e 525.

Reaction of 22 with 2. Compound **22** (9.78 mg, 0.0240 mmol) was dissolved in 5 mL of ethanol–water (1:1). After purging the solution with N$_2$ (10 min), **2** (25.42 mg, 0.1765 mmol) and then an aqueous Na$_2$S$_2$O$_4$ (30.67 mg, 0.1763 mmol) solution (1 mL) were added. The reaction mixture was stirred at room temperature (10 min) with continuous N$_2$ bubbling. Oxygen was passed through the solution (5 min) to terminate the reaction. Extraction with ethyl acetate (3 × 5 mL) followed by drying (Na$_2$SO$_4$) and evaporation of the combined organic layers in vacuo gave a violet colored solid. Preparative thick-layer chromatography of this solid in system E afforded 5.76 mg (53%) of compound **17**, R_f 0.63 (system A).

Reaction of 23 with 2. The preceding procedure was adopted using **23** (6.56 mg, 0.0161 mmol), **2** (17.05 mg, 0.1184 mmol), and an aqueous Na$_2$S$_2$O$_4$ (20.57 mg, 0.1182 mmol) solution (1 mL). Preparative thick-layer chromatography of the evaporated ethyl acetate extract in system E afforded 1.93 mg (27%) of compound **19**, R_f 0.67 (system A).

Registry No. 1, 50-07-7; 2, 35832-93-0; 4, 78-75-1; 5, 285-67-6; 6, 106-88-7; 8, 87483-16-7; 9, 87483-17-8; 10, 87483-18-9; 11a, 87483-19-0; 11b, 87508-68-7; 12, 5449-08-1; 13a, 87508-69-8; 13b, 87508-70-1; 14, 87483-20-3; *meso*-15, 87483-21-4; (*R*,R**)-15, 87483-22-5; 16, 3554-12-9; 17, 87483-23-6; 18, 87483-24-7; 19, 87483-25-8; 20, 87483-26-9; 21, 87508-71-2; 22, 87483-27-0; 23, 87483-28-1; carbonyl sulfide, 463-58-1; citric acid, 77-92-9.

# Approaches to Azepines: A New Azepine by the Photolysis of Dimethyl p-Azidosalicylate

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We have generated 3-methoxy-4-carbomethoxyphenylnitrene and 3,4-dimethoxyphenylnitrene under various conditions, in a search for new azepines. Unexpectedly, only the former, by photolysis of dimethyl p-azidosalicylate, gave an azepine. Intramolecular coordination of the nitrene to the carbonyl group being impossible, electronic rather than steric effects are implicated. The product, methyl 2,4-dimethoxy-3H-azepine-5-carboxylate was hydrolyzed to 2,3-dihydro-4-methoxy-2-oxo-1H-azepine-5-carboxylic ester and acid.

The photolysis of phenyl azide in methanol gives 2-methoxy-3H-azepine (**1** (R = H) → **2** (R = H, R′ = Me)).[1,2]

1

2
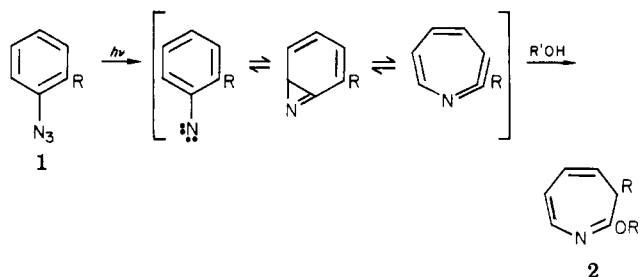
2-Alkoxyazepine production is reportedly facilitated by an electron-withdrawing group, e.g., COOMe ortho but not para to the azido group[2,3] because of an electronic effect enhancing the electrophilicity of the intermediate nitrene.[2] It has otherwise been proposed that coordination to the o-carbonyl group promotes formation of the azepine.[4] In support of the former explanation and contrary to expectation,[5] we found that methyl 4-azido-2-methoxybenzoate (dimethyl p-azidosalicylate, **3**) on photolysis in methanol gives methyl 2,4-dimethoxy-3H-azepine-5-carboxylate (**4**) in fair yield, convertible by standard methods[6,7] to the azepinones **5** (R = Me and H). No 4,7-dimethoxy isomer was detected, indicating high specificity and demonstrating the ability of a para ester group that

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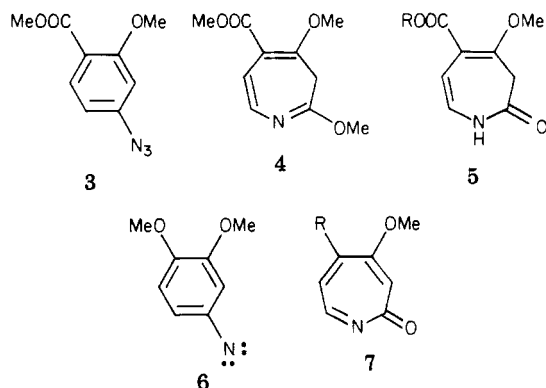(5) Smalley, R. K.; Strachan, W. A.; Suschitzky, H. *Synthesis* 1974, 503.
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cannot coordinate with the nitrene to suppress the formation of amino or azo products in favor of the azepine.

In contrast, the nitrene 6, generated photochemically from the azide, gave only the azo compound in the presence of alcohols. The generation of nitrene 6 from nitroso or nitroveratrol by deoxygenation with triphenylphosphine or diethyl methylphosphonite, in various solvents, with secondary amines[8] likewise gave no azepine, though some azoxy compound was detected spectroscopically.

Oxidation of the acid 5, (R = H) by various reagents, e.g., alkaline potassium ferricyanide, did not give clean reactions. No compound 7 (R = COOH or H) or other product useful for our azepinone work[7] was obtained.

Experimental Section

Melting points are uncorrected. ^{1}H NMR spectra were run in CDCl$_3$ (+1% Me$_4$Si) and mass spectra on the AEI MS 12 or 30 at 70 eV.

Methyl 4-Azido-2-methoxybenzoate (3). Methyl 4-amino-2-methoxybenzoate[9] (7.06 g, 29 mmol) in 42 mL of water and 7.2 mL of concentrated sulfuric acid at 0 °C was treated with a 10% solution of sodium nitrite (3.23 g, 47 mmol) portion-wise over 5 min. After stirring for 5 min at 0 °C, urea (1.44 g) was added and then 600 mg of charcoal. After $^1/_2$ h at 0 °C the solution was filtered and slowly treated with a 6% aqueous solution of sodium azide (4.29 g, 66 mmol). After 1 h the mixture was left to warm overnight to 20 °C and filtered, and the product was washed with 90 mL of cold 10% aqueous sodium carbonate solution and then 2 × 60 mL of ice–water. Yellow azide 3; 6.68 g (83%), mp 48–49 °C (methanol); IR (Nujol mull) 1725, 2120 cm^{-1}; UV (MeOH) λ_{max} nm (log ϵ) 224 (4.22), 268 (4.21), 302 (3.92); ^{1}H NMR δ 3.85 (s, 6 H), 6.47 (d, 1 H, J = 2 Hz), 6.58 (dd, 1 H, J = 2, 8 Hz), 7.77 (d, 1 H, J = 8 Hz); MS, m/e (%) 207 (M$^+$, 3), 164 (100).

Anal. Calcd for C$_9$H$_9$N$_3$O$_3$: C, 52.2; H, 4.4; N, 20.3. Found: C, 52.1; H, 4.3; N, 20.2.

Methyl 2,4-Dimethoxy-3H-azepine-5-carboxylate (4). The azide, 1 g in 920 mL of dry peroxide-free THF/dry absolute methanol (1:1), degassed (dry N$_2$, $^1/_2$ h) was irradiated (Hanovia medium-pressure Hg lamp, 150 W, Pyrex filter) under N$_2$ at 20 °C for 4 h. The solvent was removed, and the residual oil was chromatographed on 50 g of neutral alumina (14 × 2.5 cm column), eluting with 9:1 petroleum ether/benzene, followed by preparative TLC on silica gel (Kieselgel GF$_{254}$) in ether, to afford 100 mg of azepine 4 as a yellow oil (R_f 0.6) and 95 mg of recovered azide 3 (R_f 0.7).

Continued elution of the column with 85:15 petroleum ether/benzene gave after TLC 35 mg of an unstable yellow oil (R_f 0.35), possibly the 1H-azepine, and 150 mg of azepine 4, giving a 27% yield based on reacted azide. After molecular distillation: IR (film) 1130, 1230, 1320, 1440, 1630, 1715 (br), 2850, 2950, 3000 cm^{-1}; UV (MeOH) nm (log ϵ) 222 (4.36), 267 (4.02); ^{1}H NMR δ

2.85 (s, 2 H), 3.7 (s, 3 H), 3.73 (s, 3 H), 3.83 (s, 3 H), 6.18 (d, 1 H, J = 9 Hz), 6.78 (d, 1 H, J = 9 Hz); MS, m/e (%) 211 (M$^+$, 34), 155 (100).

Anal. Calcd for C$_{10}$H$_{13}$NO$_4$: C, 56.85; H, 6.2; N, 6.4. Found: C, 56.65; H, 6.15; N, 6.8.

When the experiment was repeated on the same scale after 4 $^1/_2$ h of irradiation, separation on the same column with 7:3 petroleum ether/benzene gave a new product, 61 mg, 6.5%, R_f 0.2, on TLC in ether, mp 135–138 °C, after sublimation in vacuum. This was later shown to be the azepinone 5 (R = Me), identical with the hydrolysis product of azepine 4.

Methyl 2,3-Dihydro-4-methoxy-2-oxo-1H-azepine-5-carboxylate (5, R = Me). Azide 3, 1 g in 110 mL of absolute methanol, was irradiated for 31 h as above. Similar workup gave 900 mg of a mixture of azepines/azepinone, which was hydrolyzed[6] to azepinone giving 304 mg of 5 after chromatography on 25 g of silica gel (14 × 2 cm column) with 3:1 CHCl$_3$/Et$_2$O as eluant: yield 35%, allowing for recovered azide; mp 135–138 °C sublimation; IR (KBr) 745, 1065, 1220, 1235, 1580, 1630, 1660, 1700, 2850, 2925, 3290 cm^{-1}; UV (MeOH) nm (log ϵ) 220 (3.97), 267 (3.57); ^{1}H NMR δ 3.12 (s, 2 H), 3.75 (s, 3 H), 3.9 (s, 3 H), 6.12 (m, 2 H), 8.13–8.37 (br, 1 H); MS, m/e (%) 197 (41), 155 (100).

Anal. Calcd for C$_9$H$_{11}$NO$_4$: C, 54.8; H, 5.6; N, 7.1. Found: C, 54.85; H, 5.5; N, 7.2.

3,4-Dimethoxyphenyl Azide. To a solution of 2 g (13 mmol) of 3,4-dimethoxyaniline in 14 mL water and 2.4 mL of concentrated sulfuric acid at 0 °C was added over 5 min a solution of sodium nitrite (1.076 g, 15 mmol) in 10 mL of water with stirring. After 5 min, 120 mg of urea was added over $^1/_2$ h and then 200 mg of charcoal. After $^1/_2$ h at 0 °C, the mixture was filtered and a solution of sodium azide (1.43 g, 22 mmol) in 8 mL of water was added dropwise with stirring. After 1 h the solution was left to warm to room temperature overnight. The light brown azide was filtered off and washed with 30 mL of cold 10% sodium carbonate solution and then with 3 × 20 mL of cold water. After drying over phosphorus pentoxide, the azide, 1.943 g (83%) had the following: mp 38.5–39 °C (MeOH/H$_2$O); IR (Nujol mull) 1250, 1510, 2110 cm^{-1}; UV nm (log ϵ) 212 (4.76), 258.5 (4.58), 287 (sh); ^{1}H NMR δ 3.85 (s, 6 H) 6.45–6.85 (m, 3 H); MS, m/e (%) 179 (10), 151 (100).

Anal. Calcd for C$_8$H$_9$N$_3$O$_2$: C, 53.6; H, 5.05; N, 23.45. Found: C, 53.55; H, 5.0; N, 23.55.

3,4,3′,4′-Tetramethoxyazobenzene. The azide above (827 mg) photolyzed as described gave after workup 28 mg of yellow crystals: mp 185–192 °C (benzene); IR (Nujol mull) 1240, 1260, 1500, 1590 cm^{-1}; UV nm 208 (4.02), (log ϵ) 251.5 (3.86), 372 (4.08), 383 (4.08); MS, m/e (%) 302 (14), 137 (100).

Anal. Calcd for C$_{16}$H$_{18}$N$_2$O$_4$: C, 63.55; H, 6.0; N, 9.25. Found: C, 63.8; H, 6.15; N, 8.9.

3,4-Dimethoxynitrosobenzene. To a solution of 3,4-dimethoxyaniline (382 mg, 0.1 mol) in 100 mL of chloroform containing 1.68 g of sodium bicarbonate (20 mmol) was added m-chloroperbenzoic acid (507 mg, 2.9 mmol) over 5 min. After stirring for 15 min, an equal amount of peracid was added portion-wise. After 45 min the mixture was washed with 50 mL of water containing 100 mg of sodium sulfite and 2 × 50 mL of 5% aqueous sodium bicarbonate solution. The organic phase was dried over magnesium sulfate and the solvent taken off. The oil remaining was chromatographed on 20 g of silica gel (11.5 × 2-cm column), eluting with dichloromethane, giving 88 mg (21%) of the nitroso compound; mp 52.5–55.5 °C (30–60° petroleum ether). Peracetic or Caro's acids[10] were much less effective than m-perchlorobenzoic acid.[11]

The green nitroso compound had the following: IR (KBr) 1010, 1095, 1245, 1255, 1280, 1390, 1440, 1465, 1500, 1585 cm^{-1}; UV nm (log ϵ) 207 (4.03), 214 (sh), 246.5 (3.79), 331.5 (sh), 348 (4.0); ^{1}H NMR δ 3.9 (s, 3 H), 4.05 (s, 3 H), 6.55 (d, 1 H, J = 2 Hz), 7.13 (d, 1 H, J = 2 Hz), 8.47 (dd, 1 H, J = 2, 8 Hz); MS, m/e (%) 167 (100), 137 (65), 122 (14), 107 (25).

Anal. Calcd for C$_8$H$_9$NO$_3$: C, 57.5; H, 5.45; N, 8.4. Found: C, 57.3; H, 5.45; N, 8.5.

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3,4,3′,4′-Tetramethoxyazoxybenzene. To a refluxing solution of triphenylphosphine[12] (333 mg, 1.27 mmol) in 2.5 mL of pyrrolidine was added a solution of 26.5 mg of 3,4-dimethoxynitrosobenzene (0.16 mmol) in 2.5 mL of pure ether. After $^1/_2$ h, the solution was evaporated and the residue extracted with ethanol. Evaporation of this solution and separation by TLC on silica gel/dichloromethane gave 2 mg of a yellow compound (mp 172–182 °C) considered from a comparison of its spectra with those of the azo compound to be the corresponding azoxy compound: IR (KBr) 1235, 1255 cm^{-1}; UV nm 210, 236 (sh), 251, 371, 382; MS, *m/e* (%) 318 (8), 302 (39), 137 100).

Another product, orange crystals (mp 100–115 °C; MS, *m/e* (M⁺, 238)) is thought to be *N*-(3,4-dimethoxyphenyl)-*N*-hydroxy-*N*′-aminopyrrolidine.

5-Carboxy-4-methoxy-2,3-dihydro-1*H*-azepin-2-one (5, R = H). The ester **5** (R = Me) (16 mg 0.08 mmol) in 10 mL of dry dichloromethane at −80 °C was treated with excess (1 mL) boron trichloride. After 1 h the mixture was left to warm up overnight, and volatiles were evaporated off. Methanol (10 mL) was added and volatiles were removed. This was repeated twice with 5 Ml of methanol each time, finally leaving 16 mg of free acid: mp 154–155 °C dec; IR (KBr) 1245, 1280, 1375, 1445, 1600, 1650, 1675, 2950, 3085, 3195 cm^{-1}; UV (MeOH) nm (log ε) 218 (4.27), 263 (3.83), plus OH⁻ 210 (4.26) 295 (4.16); ¹H NMR δ 3.13 (s, 2 H), 3.8 (s, 3 H), 6.02 (m, 2 H), 8.3 (br, 1 H), 12.28 (s, 1 H); MS, *m/e* (%) 183 (29), 67 (100).

Anal. Calcd for C₈H₉NO₄: C, 52.45; H, 4.96; N, 7.65. Found: C, 52.3; H, 4.85; N, 7.65.

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Chemistry of Naturally Occurring Polyamines. 7.[1] Selective Functionalization of Hydroxyputrescine
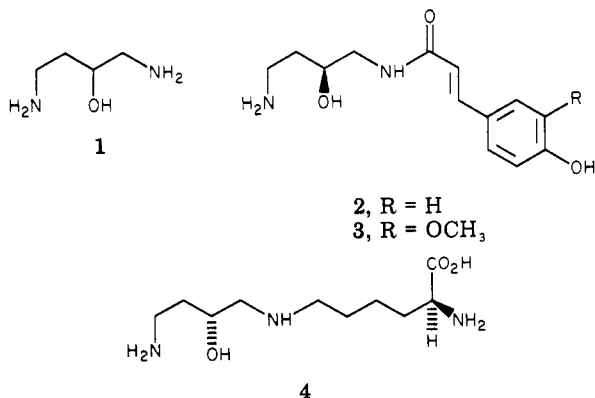
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As part of a program to synthesize biologically interesting polyamines and their conjugates, we report studies on the structure and reactivity of hydroxyputrescine–aldehyde adducts which permit regioselective functionalization of this rather rare naturally occurring diamine. When reacted with *p*-nitrobenzaldehyde (2 equiv) in CHCl₃, 1 forms predominantly **6b** (as well as **5b** and **7b**) in an equilibrium which is highly solvent dependent. The results of various regioselective acylations of the **5b/6b/7b** mixture are reported. With carbobenzoxy chloride–pyridine in CH₂Cl₂, amine **8b** forms in high yield and serves as a useful synthon for N¹-functionalized hydroxyputrescines. Total syntheses of amide **2**, an abnormal metabolite of rust-infected wheat, and of the unusual amino acid hypusine (**4**) are described by using this methodology.

Hydroxyputrescine (**1**) is an unusual, chiral polyamine that has been isolated from several strains of *Pseudomonas*.[2] Besides the parent dextrorotatory polyamine, higher conjugates of both (*R*)- and (*S*)-**1** have been found in nature. Amides **2** and **3** of hydroxyputrescine are abnormal

Table I. Solvent Dependence of the Ratio of Bis(imine) 5 and Tetrahydro-1,3-oxazine 6

solvent	5a:6a	5b:6b
pyridine-d_s	4:1	2:1
acetonitrile-d_3		1.5:1
benzene-d_6		1:2
chloroform-*d*	3:1	1:3

metabolites isolated from rust-infected wheat,[3] and the unusual amino acid hypusine (**4**), formally a conjugate between **1** and lysine,[4] has been identified in the hydrolysate of a protein which serves as a translation initiation factor in growing eucaryotic cells.[4e]

As part of a program to synthesize biologically interesting polyamines and their conjugates, we wish to report

2, R = H
3, R = OCH₃

4

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