or recrystallized. (See paragraph at the end of paper about supplementary material.)

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Registry No. 1, 87070-85-7; 2, 87070-86-8; 3 (R = Et; R' = H), 87070-87-9; 3 (R, R^1 = Me), 87088-26-4; 3 (R = Ph; R^1 = H), 87070-88-0; 3 (R, R^1 = $(CH_2)_5$), 87070-89-1; 4 (R = Et; R^1 = H), 87070-90-4; 4 (R, R^1 = Me), 87070-91-5; 5 (R = Et; R^1 = H), 87070-92-6; 5 (R, R^1 = Me), 87070-93-7; 5 (R = Ph; R^1 = H), 87070-94-8; 5 (R, R^1 = $(CH_2)_5$), 87070-95-9; 6 (R = Et; R^1 = H), 87070-96-0; 6 (R, R^1 = Me), 87070-97-1; 7 (R = Et; R^1 = H), 87070-98-2; 7 (R, R^1 = Me), 64841-63-0; 7 (R = Ph; R^1 = H), 87070-99-3; 7 (R, R^1 = $(CH_2)_5$), 87071-00-9; 8 (R = Et; R^1 = H), 87071-01-0; 8 (R, R^1 = Me), 64841-62-9; 9 (R = Et; R^1 = H), 87071-02-1; 9 (R, R^1 = Me), 50546-22-0; 9 (R = Ph; R^1 = H), 74141-11-0; 9 (R, R^1 = $(CH_2)_5$), 87071-03-2; 10 (R = Et; R^1 = H), 83726-18-5; 10 (R, R^1 = Me), 50407-79-9; 3-(trimethylsilyl)-2-propyn-1-ol tetrahydropyranyl ether, 36551-06-1; propaldehyde, 123-38-6; acetone, 67-64-1; benzaldehyde, 100-52-7; cyclohexanone, 108-94-1; (Z)-3-bromo-3-(trimethylsilyl)-2-propen-1-ol, 87071-04-3.

Supplementary Material Available: Full experimental details including scale, IR data, NMR data, and analyses for each entry in Table I and II (8 pages). Ordering information is given on any current masthead page.

Formation of Nitrosamines by Alkylation of Diazotates

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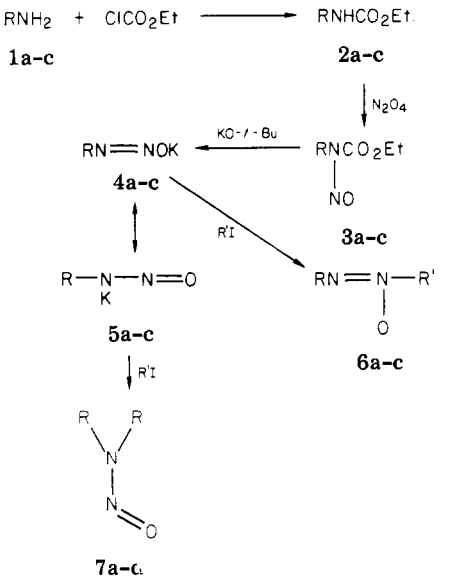
In the study of the metabolic activation of procarbazine, a chemotherapeutic agent used in the treatment of Hodgkins disease (tumors of the brain and other neoplasms), two azoxy isomers were identified as metabolites.[1-4] Further metabolism of these azoxy compounds should lead to an alkylating species.[4,5] A regiospecific synthesis of each of these unsymmetrical compounds or their unsubstituted analogues was desired to provide an opportunity to study the metabolism of the individual azoxy isomers to determine their relative importance. Moss and co-workers have reported that alkylation of diazotates can be used for the regiospecific synthesis of unsymmetrical azoxyalkanes.[6] Attempts were made to prepare the individual azoxy isomers benzyl-*NNO*-azoxymethane (**6a**) and benzyl-*ONN*-azoxymethane (**6b**) by using this methodology, but with THF rather than HMPA as the solvent (see Scheme I). The *N*-nitrosourethane **3a** used in these reactions was prepared by the sequence shown in Scheme I. The *N*-nitrosourethane **3a** was then used to generate the diazotate in situ. The diazotate was prepared by reaction of **3a** with KO-*t*-Bu (2 equiv) in dry THF under N_2 at −30 °C followed by alkylation with methyl iodide at 35 °C.

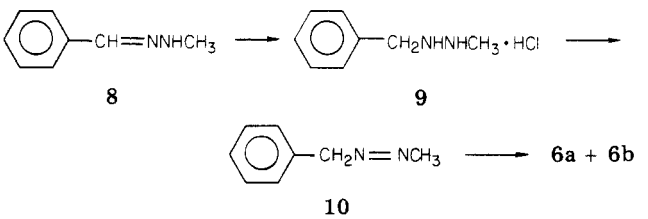
In the case of **6b** the diazotate was generated from *N*-methyl-*N*-nitrosourethane (**3b**), which was obtained by the sequence shown in Scheme I. The diazotate was generated in situ by the method described above and was alkylated with benzyl iodide at 35 °C.

Scheme I[a]



[a] a, R = $C_6H_5CH_2$, R' = CH_3; b, R = CH_3, R' = $C_6H_5CH_2$; c, R = $C_6H_5(CH_3)CH$, R' = CH_3CH_2; d, R = CH_3CH_2, R' = $C_6H_5(CH_3)CH$.

Scheme II



When the alkylation product from the reaction of the diazotate from **3a** with methyl iodide and the product from the reaction of the diazotate of **3b** with benzyl iodide were compared they were found to be the same. Both products had GC retention times of t_R = 28.0 min.[7a] The two products also had identical ^1H NMR spectra and were observed as a mixture of two isomers. One isomer had chemical shifts at δ 2.85 (s, 3 H), 4.79 (s, 2 H), and 7.30 (s, 5 H), and a second isomer with chemical shifts at δ 3.59 (s, 3 H), 5.28 (s, 2 H), and 7.31 (s, 5 H) was also observed. The isomers were in a ratio of 78/22. These chemical shift values were found to be identical with those reported for the syn and anti isomers of benzylmethylnitrosamines **7a** and **7b**, and the reported syn/anti isomer ratio (79/21), was also the same.[8] A sample of benzylmethylnitrosamines **7a,b** was prepared by nitrosation of *N*-methylbenzylamine with aqueous $NaNO_2$ in acetic acid.[9] The GC retention time of this authentic sample of benzylmethylnitrosamine was also found to be t_R = 28.0 min.[7a]

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(7) (a) On a 6 ft × 4 mm i.d. column with 3% OV-225 on 100/120 Supelcoport at 90–135 °C at 1 °C/min. (b) Same as ref. 11a except 90–135 °C at 10 °C/min.
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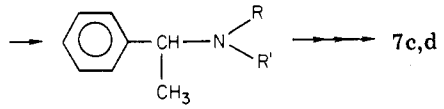
Scheme III



11, R = H; R' = $OCOCH_2C_6H_5$
12, R = Et; R' = $OCOCH_2C_6H_5$
13, R = Et; R' = H·HCl

The desired azoxyalkanes **6a** and **6b** were prepared as a mixture by the alternate route shown in Scheme II. The azoxy isomers **6a** and **6b** were obtained as a 1:1 mixture in 75% yield by oxidation of **10** in CH_2Cl_2 with *m*-chloroperbenzoic acid.[10] The ^1H NMR spectral of data **6a** and **6b** were δ 3.15 (s, 3 H), 5.25 (s, 2 H), and 7.33 (s, 5 H) and δ 4.05 (s, 3 H), 4.57 (s, 2 H), and 7.36 (s, 5 H), in a ratio of 48/52, respectively. These chemical shift values are the same as those previously reported for these azoxy isomers; since the method of preparation was different the isomer ratios could not be compared.[11] The GC retention times of **6a** and **6b** at t_R = 14.8 and 21.2 min, respectively, were distinctly different than those of the nitrosamines **7a,b** under the same conditions.[7a]

The alkylation of diazotates from **3a** and **3b** lead to nitrosamines **7a,b,** and the azoxyalkanes **6a** and **6b** were not observed. Even examination of the crude reaction mixtures of these diazotate alkylations by GC revealed no peaks corresponding to the observed retention times of the azoxyalkanes. A GC peak at t_R = 3.4 min was observed and was identified as *tert*-butyl ethyl carbonate.[7a]

Because of the formation of nitrosamines in these reactions an attempt was made to prepare the azoxyalkane **6c** which Moss and Landon had made by the alkylation of the diazotate **4c** with ethyl iodide in HMPA or with triethyloxonium tetrafluoroborate in CH_2Cl_2.[6c,12] The diazotate was prepared in situ by reaction of the N-nitrosourethane **3c** with KO-*t*-Bu at −30 °C in dry THF under N_2.[6] The reaction sequence for the preparation of **3c** is summarized in Scheme I. Alkylation of **4c** with ethyl iodide in THF at 35 °C for 8 h gave a 40% yield of product after the workup and preparative layer chromatography. The ^1H NMR spectra of the broad band at R_f 0.45 showed two compounds to be present. The first compound, **6c**, was 70% of the mixture with signals at δ 1.46 (d, 3 H, J = 6.7 Hz), 1.48 (t, 3 H, J = 7.3 Hz), 4.18 (q, 2 H, J = 7.3 Hz), 5.14 (q, 1 H, J = 6.7 Hz), and 7.31 (m, 5 H). The azoxy compound **6c** was isolated in 28% yield. These chemical shifts were the same as those reported by Moss for **6c**.[12] They reported that alkylation with ethyl iodide in HMPA led to **6c** in 28% yield, and alkylation with triethyloxonium tetrafluoroborate in CH_2Cl_2 led to **6c** in 46% yield. In view of the results obtained for the other diazotate alkylations, it was suspected that the second compound was the nitrosamine isomers **7c,d.** The second compound, **7c,d**, was 30% of the mixture and had signals at δ 0.90 (t, 3 H, J = 7.1 Hz), 1.84 (d, 3 H, J = 7.1 Hz), 3.33 (m, 2 H, J = 7.1 Hz),[13] 5.70 (q, 1 H, J = 7.1 Hz), 7.31 (m, 5 H). The nitrosamine **7c,d** was isolated in 12% yield. To verify the identity of the second compound an independent synthesis of **7c,d** was carried out. The amine **1c** was protected as its carbobenzoxy derivative, giving **11** in 73% yield[14] (Scheme III). Reaction of **11** with NaH followed by alkylation with ethyl iodide gave **12** in 88% yield. The carbobenzoxy protecting group was then removed with HCl in glacial acetic acid, leading to the hydrochloride salt **13** in 74% yield.[15] The salt **13** was then nitrosated, giving **7c,d** in 60% yield.[9] The ^1H NMR spectra of **7c,d** showed both *syn*-**7c,** and *anti*-**7d** isomers in a ratio of 81/19, respectively. The isomer **7c** had signals at δ 0.90 (t, 3 H, J = 7.1 Hz), 1.84 (d, 3 H, J = 7.1 Hz), 3.33 (m, 2 H, J = 7.1 Hz),[13] 5.70 (q, 1 H, J = 7.1 Hz), and 7.31 (m, 5 H), confirming that the second compound **7c** was indeed the nitrosamine. The isomer **7d** had signals at δ 1.25 (t, 3 H, J = 7.2 Hz), 1.49 (d, 3 H, J = 7.1 Hz), 3.81 (m, 2 H, J = 7.2 Hz), 6.13 (q, 1 H, J = 7.1 Hz), 7.34 (m, 5 H). This isomer was in too low a concentration in the diazotate alkylation product to be observed by ^1H NMR. Analysis of the diazotate alkylation product by GC showed two peaks at t_R = 6.4 min (70% of the mixture) and at t_R = 12.6 min (30% of the mixture.[7b] The independently prepared nitrosamines **7c,d** gave a single GC peak at t_R = 12.6 min, the same as the second product of the diazotate alkylation.[7b]

These investigations have shown that the alkylation of even highly substituted diazotates in THF leads to the formation of nitrosamines, 30% of the isolated product in the case examined, in addition to the expected azoxyalkane. Moss and co-workers have observed the predominance of the nitrosamine formation when diazotates are alkylated in a 95:5 ether–HMPA solution, and Müller and co-workers obtained high yields of nitrosamide when diazotates were acylated in ether solutions.[16,17] The azoxyalkanes such as **6c** are derived by attack of N-2, via **4c**, on the alkyl halide. The nitrosamines such as **7c,d**, on the other hand, arise by attack of N-1, via **5c**, on the alkyl halide. When less sterically hindered diazotates were generated, the alkylation was much more selective. In cases such as **3a** and **3b** attack of N-1, via **5a** or **5b**, on the alkyl halide was the only observed reaction, leading exclusively to formation of nitrosamine **7a** or **7b**.

Experimental Section

Hexane was dried over $LiAlH_4$ and was distilled under N_2. THF was predried over CaH_2, dried over $LiAlH_4$, and distilled under N_2. Acetone was dried over K_2CO_3 and distilled. Melting points are uncorrected and were obtained on a Fisher-Johns melting point apparatus. Mass spectra were obtained on a Finnigan 4023-gc-ms-ds operated in the chemical-ionization mode with isobutane as the reagent gas. NMR spectra were obtained on a Varian FT-80 spectrometer. Chemical shifts are reported relative to Me_4Si (δ 0). Gas chromatography was done on a Varian Aerograph 2100 gas chromatograph, equipped with a flame-ionization detector. Preparative layer chromatography was performed on 2-mm-thick 20 cm × 20 cm silica gel 60 F_{254} plates.

Urethane 2a. The urethane **2a** was prepared by the method of Kurtz and Niemann by reaction of benzylamine with ethyl chloroformate in ether and aqueous sodium hydroxide at 0 °C.[18] The product **2a** was isolated: 75% yield; mp 43–44 °C (lit.[18] mp 44 °C); ^1H NMR ($CDCl_3$) δ 1.21 (t, 3 H, J = 7.2 Hz), 4.08 (q, 2 H, J = 7.2 Hz), 4.30 (d, 2 H, J = 6.0 Hz), 5.14 (br m, 1 H), 7.26 (s, 5 H).

***N*-Nitrosourethane 3a.** The *N*-nitrosourethane **3a** was prepared by reaction of the urethane **2a** with N_2O_4 in ether with $NaHCO_3$ at −30 °C for 1 h.[19] The *N*-nitrosourethane **3a** was

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prepared by reaction of the urethane **2a** with N_2O_4 in ether with $NaHCO_3$ at −30 °C for 1 h.[19] The reaction mixture was neutralized with 10% aqueous $NaHCO_3$. The aqueous layer was extracted with ether (3 × 40 mL). The combined organic layers were dried over $MgSO_4$. The solvent was removed under reduced pressure. The product was distilled under vacuum, giving a yellow oil: 45% yield; bp 63–65 °C (2 torr); ^1H NMR ($CDCl_3$) δ 1.43 (t, 3 H, J = 7.2 Hz), 4.54 (q, 2 H, J = 7.2 Hz), 4.90 (s, 2 H), 7.22 (s, 5 H).

Urethane 2b. The urethane **2b** was prepared by the same method as urethane **2a** except that 40% aqueous methylamine was used in place of the benzylamine. The product was isolated by vacuum distillation, giving **2b** as a clear colorless oil: bp 75–76 °C (15 torr); ^1H NMR ($CDCl_3$) δ 1.24 (t, 3 H, J = 7.1 Hz), 2.78 (s, 3 H), 4.11 (q, 2 H, J = 7.1 Hz), 5.10 (br s, 1 H).

***N*-Nitrosourethane 3b.** The *N*-nitrosourethane **3b** was prepared by the same method as the *N*-nitrosourethane **3a**. The product was isolated as a clear yellow oil after vacuum distillation: bp 65–66 °C (13 torr); ^1H NMR ($CDCl_3$) δ 1.46 (t, 3 H, J = 7.1 Hz), 3.15 (s, 3 H), 4.55 (q, 2 H, J = 7.1 Hz).

General Diazotate Alkylation Procedure. An oven-dried round-bottomed flask with a septum inlet, pressure-equalized addition funnel, and gas stopcock was evacuated and purged with N_2. The reaction was run under a positive N_2 atmosphere. The flask was charged with 1.0 g (9.0 mmol) of KO-*t*-Bu and 7 mL of dry THF. The reaction mixture was cooled to −30 °C in a dry-ice/*i*-PrOH bath and 1.0 g (4.5 mmol) of the *N*-nitrosourethane in 8 mL of dry THF was added dropwise with stirring. The reaction mixture was then stirred at 25 °C for 1 h. The alkyl iodide (6.0 mmol) in 10 mL of dry THF was added dropwise with stirring at 25 °C. The reaction mixture was then stirred at 35 °C for 24 h. The reaction mixture was then poured into 50 mL of ice–brine solution. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were then dried over $MgSO_4$. The solvent was removed under reduced pressure, giving the product as a clear yellow oil.

Alkylation of the Diazotate from 3a. The diazotate from the *N*-nitrosourethane **3a** was prepared by the procedure described above. The diazotate was then alkylated with methyl iodide. After the workup procedure described above, the product was dried on a vacuum pump at 1 torr. The product a clear yellow oil was isolated: 35% yield; ^1H NMR ($CDCl_3$) δ 2.85 (s, 3 H), 4.79 (s, 2 H), 7.30 (s, 5 H) and 3.59 (s, 3 H), 5.28 (s, 2 H), 7.31 (s, 5 H); mass spectrum, m/z (relative intensity) 151 (50, MH^+), 91 (100, $C_7H_7^+$).

Alkylation of the Diazotate from 3b. The diazotate from the *N*-nitrosourethane **3b** was prepared by the procedure described above. The diazotate was then alkylated with benzyl iodide.[20] After the workup procedure described above, the product was dried on a vacuum pump at 1 torr. The product was a clear yellow oil: 33% yield; ^1H NMR ($CDCl_3$) δ 2.85 (s, 3 H), 4.79 (s, 2 H), 7.30 (s, 5 H), 3.59 (s, 3 H), 5.28 (s, 2 H), 7.31 (s, 5 H); mass spectrum, m/z (relative intensity) 151 (43, MH^+), 91 (100, $C_7H_7^+$).

Benzyl Iodide. The benzyl iodide was prepared by the method of Miller and Nunn.[20] Benzyl chloride in acetone was treated with NaI and a catalytic amount of anhydrous $FeCl_3$. The product was stored at −30 °C.

Benzylmethylnitrosamines (7a,b). The isomers of benzylmethylnitrosamine were prepared by the reaction of *N*-methylbenzylamine with $NaNO_2$ in water and CH_3CO_2H for 30 min.[9] After neutralization with 5 N NaOH, the reaction mixture was extracted with ether and dried over Na_2SO_4. The solvent was removed under reduced pressure, giving the product as a clear yellow oil: 72% yield; ^1H NMR ($CDCl_3$) δ 2.85 (s, 3 H), 4.79 (s, 2 H), 7.30 (s, 5 H), 3.59 (s, 3 H), 5.28 (s, 2 H), 7.31 (s, 5 H); mass spectrum, m/e (relative intensity) 151 (46, MH^+), 136 (19, MH–CH_3^+), 91 (100, $C_7H_7^+$).

1-Benzylidene-2-methylhydrazine (8). A round-bottomed flask with a pressure-equalized addition funnel was evacuated and flushed with N_2. The reaction was run under a positive N_2 atmosphere. The flask was charged with 10.2 mL (0.10 mol) of freshly distilled benzaldehyde and 100 mL of benzene. To this was added dropwise with stirring a solution of 8.0 mL (0.15 mol) of methylhydrazine in 50 mL of benzene. After the addition was complete, the addition funnel was replaced with a Dean–Stark trap and condenser. The reaction mixture was heated under reflux with azeotropic removal of water. After the theoretical amount of water was removed, the reaction mixture was cooled to 25 °C and was dried over Na_2SO_4. The solvent was removed under reduced pressure, and the product was distilled under vacuum. The product was a clear pale yellow oil: 11.4 g (85% yield); bp 79–80 °C (0.7 torr) [lit.[21] bp 107 °C (0.2 torr)]; ^1H NMR ($CDCl_3$) δ 2.83 (s, 3 H), 5.58 (s, 1 H), 7.28 (m, 6 H).

1-Benzyl-2-methylhydrazine Hydrochloride (9). The hydrazine hydrochloride was prepared by a modification of the method of Nair and Sinhababu.[22] The methylbenzylidenehydrazine (**8**; 4.8 g 35.9 mmol) was dissolved in 150 mL of methanol. To this were added 0.5 mg of methyl red indicator and 2.8 g (45.0 mL) of sodium cyanoborohydride. The reaction mixture was stirred at 25 °C, and 12 M HCl was added dropwise at a rate to maintain pH 4 by observing the color change of the indicator. After 48 h the excess hydride was destroyed by the addition of 3 mL of 12 M HCl. The indicator was removed by the addition of activated carbon. The white precipitate and activated carbon were removed by filtration. The solvent was removed under reduced pressure. The residue was recrystallized twice from 1:1 methanol/ethanol with addition of ether to the cloud point. The product **9** (a white solid) was isolated by suction filtration: 55% yield; mp 143–145 °C (lit.[23] mp 141–143 °C); ^1H NMR (Me_2SO-d_6) δ 2.66 (s, 3 H), 4.30 (s, 2 H), 7.38 (s, 5 H), 8.90 (br s, 3 H); mass spectrum, m/z (relative intensity) 137 (100, M^+ − Cl).

Benzylazomethane 10. The azo compound **10** was prepared by the method of Tsolis et al.[24] The hydrochloride salt **9** was neutralized with base and oxidized with HgO in CH_2Cl_2. The product was isolated by filtration and removal of the solvent under reduced pressure. The product was a clear colorless oil isolated in 72% yield by vacuum distillation from a micromolecular still: 67–72 °C (oil bath temperature; 40 torr); ^1H NMR ($CDCl_3$) δ 3.77 (t, 3 H, J = 1.3 Hz), 4.90 (q, 2 H, J = 1.3 Hz), 7.32 (s, 5 H).

Methylbenzyl Azoxy Isomers 6a,b. The methylbenzyl azoxy isomers **6a** and **6b** were prepared by an adaptation of the method of Brough et al.[10] The azo compound **10** was oxidized with *m*-chloroperbenzoic acid in CH_2Cl_2 for 20 h. The products were isolated as a yellow oil in 65% yield after purification by preparative layer chromatography on silica gel plates. The plates were developed with CH_2Cl_2. The band with R_f 0.41 was cut out and eluted with 3% EtOAc/CH_2Cl_2: ^1H NMR ($CDCl_3$) for **6a** δ 3.15 (s, 3 H), 5.25 (s, 2 H), 7.33 (s, 5 H); for **6b** δ 4.05 (s, 3 H), 4.57 (s, 2 H), 7.36 (s, 5 H); mass spectrum, m/z (relative intensity) 151 (100, MH^+), 135 (25, MH–O^+), 91 (6) $C_7H_7^+$).

Urethane 2c. The urethane **2c** was prepared by the same method as urethane **2a** except that α-methylbenzylamine was used in place of benzylamine. The product was a clear colorless oil isolated in 84% after vacuum distillation: bp 108–110 °C (1.4 torr); ^1H NMR ($CDCl_3$) δ 1.18 (t, 3 H, J = 7.1 Hz), 1.43 (d, 3 H, J = 6.8 Hz), 4.07 (q, 2 H, J = 7.1 Hz), 4.81 (m, 1 H, J = 6.8 Hz), 5.25 (br d, 1 H) 7.28 (s, 5 H); mass spectrum, m/z (relative intensity) 194 (100, MH^+), 178 (6, MH–CH_4^+), 120 (14, MH–HCO_2Et).

***N*-Nitrosourethane 3c.** The nitrosourethane **3c** was prepared by the same method as **3a** except that the urethane **2c** was used in place of the urethane **2a**. The product was as a clear yellow oil after distillation under vacuum: 45% yield; bp 63–65 °C (2 torr); ^1H NMR ($CDCl_3$) δ (syn and anti isomers) 1.26 (t, 3 H, J = 7.1 Hz), 1.56 (d, 3 H, J = 6.6 Hz), 4.14 (q, 2 H, J = 7.1 Hz), 5.71 (q, 1 H, J = 6.6 Hz), 7.23 (m, 5 H) and 1.29 (t, 3 H, J = 7.1 Hz) 1.61 (d, 3 H, J = 7.1 Hz), 4.38 (q, 2 H, J = 7.1 Hz), 6.05 (q, 1 H, J = 7.1 Hz), 7.33 (m, 5 H); mass spectrum, m/z (relative intensity) 223 (17, MH^+), 194 (60, MH–NO^+), 105 (100, $CH_3C_7H_6^+$).

Alkylation of the Diazotate from 3c. The diazotate of the *N*-nitrosourethane **3c** was prepared by the procedure described above. The diazotate was then alkylated with ethyl iodide. After

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the workup procedure described above, the product was purified by preparative layer chromatography. The product was chromatographed on silica gel plates which were developed with CH_2Cl_2. The band with R_f 0.46 was cut out and eluted with 3% $MeOH/CH_2Cl_2$, giving the product as a yellow oil: 40% yield; ^1H NMR ($CDCl_3$) for **7c** δ 0.90 (t, 3 H, J = 7.1 Hz), 1.84 (d, 3 H, J = 7.1 Hz), 3.33 (q, 2 H, J = 7.1 Hz), 5.70 (q, 1 H, J = 7.1 Hz), 7.32 (m, 5 H); for **6c** δ 1.46 (d, 3 H, J = 6.7 Hz), 1.48 (t, 3 H, J = 7.3 Hz), 4.18 (m, 2 H, J = 7.3 Hz), 5.14 (q, 1 H, J = 6.7 Hz), 7.31 (m, 5 H); mass spectrum, m/z (relative intensity) 179 (100, MH^+), 163 (7, $MH\text{-}O^+$), 121 (7), 105 (50, $C_7H_8CH_3^+$).

***N*-Carbobenzoxy-α-methylbenzylamine (11).** The protected amine **11** was prepared by reaction of α-methylbenzylamine in ether/water with an ether solution of benzyl chloroformate and NaOH at 0 °C for 1 h.[14] The reaction mixture was then stirred at 25 °C for 3 h. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 40 mL). The combined organic layers were dried over Na_2SO_4. The solvent was removed under reduced pressure and the product, a white solid, was dried in vacuo at 2 torr. The product **11** was isolated: 54% yield; mp 57–58 °C; ^1H NMR ($CDCl_3$) δ 1.46 (d, 3 H, J = 6.7 Hz), 4.92 (m, 1 H, J = 6.7 Hz), 5.01 (br s, 1 H), 5.07 (s, 2 H), 7.30 (s, 10 H); mass spectrum, m/z (relative intensity) 256 (100, MH^+), 152 (65, $MH^+ - CO_2CH_2C_6H_5$), 105 (64, $CH_3C_7H_6^+$).

***N*-Ethyl-*N*-carbobenzoxy-α-methylbenzylamine (12).** An oven-dried round-bottomed flask with a septum inlet, pressure-equalized addition funnel, and gas stopcock was evacuated and purged with N_2. The reaction was run under a positive N_2 atmosphere. The flask was charged with 0.8 g (17.0 mmol) of NaH which was washed with 15 mL of dry hexane. The NaH was covered with 5 mL of dry THF. The reaction mixture was cooled in an ice bath and 4.0 g (15.6 mmol) of the amine **11** in 20 mL of dry THF was added dropwise with stirring. After the addition was complete, the reaction mixture was stirred at 25 °C for 1.5 h. The reaction mixture was cooled with an ice bath, and 1.26 mL (15.8 mmol) of ethyl iodide in 10 mL of dry THF was added dropwise with stirring. After the addition was complete, the reaction mixture was stirred at 25 °C for 3 days. The reaction mixture was poured into 50 mL of saturated NaCl solution. The layers were separated, and the aqueous layer was extracted with ether (3 × 40 mL). The combined organic layers were dried over $MgSO_4$. The solvent was removed under reduced pressure. The product was a clear colorless oil: 3.89 g (88% yield); ^1H NMR ($CDCl_3$) δ 0.96 (t, 3 H, J = 7.0 Hz), 1.53 (d, 3 H, J = 7.1 Hz), 3.04 (q, 2 H, J = 7.0 Hz), 5.18 (s, 2 H), 5.54 (q, 1 H, J = 7.1 Hz), 7.28 (s, 5 H), 7.32 (s, 5 H); mass spectrum, m/z (relative intensity) 284 (100, MH^+), 180 (17), 148 (16).

***N*-Ethyl-α-methylbenzylamine Hydrochloride (13).** A flask with a gas inlet tube and a gas stopcock attached to a gas trap was charged with 0.50 g (1.7 mmol) of the protected amine **13** and 4 mL of glacial acetic acid.[15] The solution was continuously saturated with hydrogen chloride for 1 h. After the addition was complete, the reaction mixture was stirred at 25 °C for 1 h. The reaction mixture was diluted with ether. The resulting white precipitate was isolated by suction filtration. The filter cake was washed with ether (2 × 20 mL). The product was dried in vacuo at 2 torr and isolated: 40% yield; mp 198–199 °C (lit.[25] mp 199–200 °C); ^1H NMR (me_2SO-d_6) δ 1.19 (t, 3 H, J = 7.2 Hz), 1.58 (d, 3 H, J = 6.8 Hz), 2.67 (q, 2 H, J = 7.2 Hz), 4.40 (q, 1 H, J = 7.2 Hz), 7.47 (m, 5 H), 9.02 (br s, 2 H); mass spectrum, m/z (relative intensity) 150 (100, MH^+), 134 (11, $MH^+ - CH_4$), 105 (7, $CH_3C_6H_7^+$).

***N*-Nitroso-*N*-ethyl-α-methylbenzylamine (7c,d).** A flask was charged with 0.12 g (0.90 mmol) of the amine salt **13** which was dissolved in 840 μL of water and 120 μL of glacial acetic acid.[9] The reaction mixture was stirred at 25 °C, and 120 mg (2.61 mmol) of $NaNO_2$ dissolved in 300 μL of water was added dropwise over a period of 10 min. After the addition was complete, the reaction was stirred at 25 °C for 30 min. The reaction mixture was cooled in an ice bath and was treated with 500 μL of 5 M NaOH. The reaction mixture was extracted with ether (4 × 3 mL). The combined organic layers were dried over Na_2SO_4. The solvent was removed under reduced pressure, giving the product as an oil: 96 mg (60% yield); ^1H NMR ($CDCl_3$) for isomer **7c** δ 0.91 (t, 3 H, J = 7.1 Hz), 1.86 (d, 3 H, J = 7.1 Hz), 3.39 (m, 2 H, J = 7.1 Hz), 5.63 (q, 1 H, J = 7.1 Hz), 7.34 (m, 5 H); for isomer **7d** δ 1.25 (t, 3 H, J = 7.2 Hz), 1.49 (d, 3 H, J = 7.1 Hz), 3.81 (dq, 2 H, J = 7.2 Hz), 6.13 (q, 1 H, J = 7.1 Hz), 7.34 (m, 5 H); mass spectrum, m/z (relative intensity) 179 (91, MH^+), 105 (100, $CH_3C_7H_6^+$).

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Registry No. **1a**, 100-46-9; **1b**, 74-89-5; **1c**, 98-84-0; **2a**, 2621-78-5; **2b**, 105-40-8; **2c**, 1623-51-4; **3a**, 6558-76-5; **3b**, 615-53-2; **3c**, 6316-19-4; **4a**, 87014-46-8; **4b**, 87039-32-5; **4c**, 26370-44-5; **6a**, 87014-47-9; **6b**, 87014-48-0; **6c**, 26370-70-7; **7a**, 937-40-6; **7c**, 87014-49-1; **8**, 13466-29-0; **9**, 26253-98-5; **10**, 7737-14-6; **11**, 87014-50-4; **12**, 87014-51-5; **13**, 37771-39-4; ethyl chloroformate, 541-41-3; methyl iodide, 74-88-4; benzyl iodide, 620-05-3; *N*-methylbenzylamine, 103-67-3; benzaldehyde, 100-52-7; methylhydrazine, 60-34-4; ethyl iodide, 75-03-6.

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Nucleophilic Aromatic Substitution by 3-Amino-2-butenoates

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The utility of 3-amino-2-butenoates in the preparation of 5-hydroxyindoles from quinones is well-established.[1-3] The mechanism of this transformation, as illustrated for reaction of benzoquinone (**1**) with ethyl 3-amino-2-butenoate (**2**), apparently involves nucleophilic attack by C-2 of the olefin to afford **3**, which subsequently cyclizes to give indole **4** (Scheme I). Analogous Nenitzescu-type reactions have been carried out on maleimides[4] and 3-acylchromones.[5] However, Buckler et al.[6] have recently shown that treatment of aryl acid chlorides with 3-amino-2-butenoates gives both N-acetylated and C-2-acetylated products.

As part of a synthetic program directed at the preparation of novel nitroheterocycles to serve as hypoxic cell radiosensitizers,[7] we have studied the reaction between 3-amino-2-butenoates and some halo nitro aromatics. Our intent was to prepare vinylogous amines of these nitro aromatics by displacement of halogen, as exemplified in the Nenitzescu process. Since the potency of nitro aromatics, as hypoxic cell radiosensitizers, increases with increasing stability of the molecular radical anion,[7] it was anticipated that this structural modification should enhance pharmacologic activity by increasing conjugative stabilization of the radical anion.

Results and Discussion

We have found that 3-amino-2-butenoates react with nitro aromatics that possess easily displaceable halides to give the corresponding vinylogous amines. For example,

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