THF was treated with *tert*-butyllithium (3.8 mL of 2.0 M solution in pentane, 7.6 mmol) at −78 °C. After the mixture was stirred for 90 min, trimethylsilyl chloride (0.60 mL, 0.52 g, 4.8 mmol) was injected by syringe. The reaction mixture was stirred for 4.5 h and then transferred at 0 °C in air to a one-neck flask. The solvent was removed under vacuum. Column chromatography (base-washed silica gel, hexane) yielded 0.88 g (91%) of a colorless oil: ^{1}H NMR (CCl_4) δ 7.20–7.32 (m, 5 H, Ph), 6.13 (s, 1 H, C4-H of furan), 2.31 (s, 3 H, $ArCH_3$), 0.21 (s, 9 H, $Si(CH_3)_3$); IR (neat) 2950, 1590, 1485, 1435, 1242, 832, 730 cm^{-1}; mass spectrum, *m/e* 262 (M^+, 100%), 187, 173; exact mass calcd for $C_{14}H_{18}OSSi$ 262.0848, found 262.0850.

2-(Phenylthio)-3-(trimethylsilyl)-5-octylfuran was prepared by an analogous procedure as a colorless oil: ^{1}H NMR (CCl_4) δ 7.13 (m, 5 H, Ph), 6.04 (s, 1 H, C4-H of furan), 2.65 (t, J = 7 Hz, $CH_2C_7H_{15}$), 1.67 (br m, 2 H, $CH_2C_6H_{13}$), 1.30 (m, 10 H, $(CH_2)_5CH_3$), 0.90 (br t, J = 7 Hz, CH_2CH_3), 0.21 (s, 9 H, $Si(CH_3)_3$); IR (neat) 2930, 1585, 1480, 1255, 840 cm^{-1}; mass spectrum, *m/e* 360 (M^+), 345 ($M^+ - CH_3$), 262 (100%, $M^+ - C_7H_{14}$), 261 ($M^+ - C_7H_{15}$), 73; exact mass calcd for $C_{21}H_{32}OSSi$ 360.1946, found 360.1949.

2-(Phenylthio)-5-methylfuran-3-carboxylic Acid. To 2-(phenylthio)-3-bromo-5-methylfuran (0.69 g, 2.5 mmol) in THF (40 mL) at −78 °C was added *tert*-butyllithium (2.6 mL of 2.0 M solution in pentane, 5.1 mmol). After the solution was stirred for 1 h, carbon dioxide from a cylinder was passed in for 5 min. The solution was warmed to room temperature and partitioned between 2 N sodium hydroxide solution and pentane. The organic layer was extracted with more sodium hydroxide solution. The combined aqueous layer was shaken with 1:1 diethyl ether–pentane, acidified with excess 2 N hydrochloric acid solution, and extracted with diethyl ether (5 × 20 mL). The ether layer was washed with brine, dried ($MgSO_4$), and filtered, and the solvent removed under vacuum. Recrystallization from hexane afforded 0.413 g (52%) of colorless plates: mp 121.0–122.0 °C; ^{1}H NMR ($CDCl_3$) δ 7.33 (m, 5 H, Ph), 6.47 (s, 1 H, C4-H of furan), 2.27 (s, 3 H, CH_3); IR (neat) 3200, 3050, 2950, 1683, 1517, 1250, 713 cm^{-1}; mass spectrum, *m/e* 234 (M^+, 100%), 191, 173, 146, 105, 43. Anal. Calcd for $C_{12}H_{10}O_3S$: C, 61.59; H, 4.27. Found: C, 61.72; H, 4.36.

2-Butyl-4-octylfuran. A suspension of 1.66 g of Raney nickel in 60 mL of ethanol containing 0.29 g (0.083 mmol) of dissolved 2-(phenylthio)-3-octyl-5-butylfuran was heated at reflux for 6 h. The reaction mixture was filtered through Celite and the solvent evaporated under vacuum. Kugelrohr distillation (100–115 °C, 0.15 mm) yielded 0.16 g (83%) of a colorless oil: ^{1}H NMR (CCl_4) δ 6.95 (s, 1 H, C5-H of furan), 5.75 (s, 1 H, C3-H of furan), 2.53 (t, J = 7 Hz, 2 H, $CH_2C_3H_7$), 2.30 (t, J = 7 Hz, 2 H, $CH_2C_7H_{15}$), 1.29 (m, 16 H, $(CH_2)_2CH_3$ and $(CH_2)_6CH_3$), 0.91 (br t, J = 7 Hz, 3 H, CH_3), 0.87 (t, J = 7 Hz, 3 H, CH_3); IR (neat) 2950, 2910, 2850, 1605, 1530, 1460, 1110, 940 cm^{-1}; mass spectrum, *m/e* 236 (M^+), 138 ($M^+ - C_7H_{14}$), 74, 59 (100%). Anal. Calcd for $C_{16}H_{28}O$: C, 81.29; H, 11.94. Found: C, 81.43; H 12.25.

2-Methyl-4-(trimethylsilyl)furan was prepared by the same desulfurization procedure, starting from 2-(phenylthio)-3-(trimethylsilyl)-5-methylfuran. It was a colorless liquid: bp 75 °C (175 mm, Kugelrohr); ^{1}H NMR (CCl_4) δ 7.21 (s, 1 H, C5-H of furan), 5.95 (s, 1 H, C3-H of furan), 2.25 (s, 3 H, $ArCH_3$), 0.19 (s, 9 H, $Si(CH_3)_3$); IR (neat) 2890, 1580, 1470, 1240, 835 cm^{-1}; mass spectrum, *m/e* 154 (M^+), 139 (100%, $M^+ - CH_3$ of silyl group), 73 ($SiMe_3^+$), 43; exact mass calcd for $C_8H_{14}OSi$ 154.0814, found 154.0810.

2-Octyl-4-(trimethylsilyl)furan was prepared as a colorless oil by a similar desulfurization of 2-(phenylthio)-3-(trimethylsilyl)-5-octylfuran: ^{1}H NMR (CCl_4) δ 7.15 (s, 1 H, C5-H of furan), 5.91 (s, 1 H, C3-H of furan), 2.61 (t, J = 7 Hz, 2 H, $CH_2C_7H_{15}$), 1.63 (m, 2 H, $CH_2C_6H_{13}$), 1.33 (m, 10 H, $(CH_2)_5CH_3$), 0.90, (t, 3 H, CH_2CH_3), 0.23 (s, 9 H, $Si(CH_3)_3$); IR (neat) 2920, 2850, 1580, 1250, 1110, 840 cm^{-1}; mass spectrum, *m/e* 252 (M^+), 237 ($M^+ - CH_3$ of silyl group), 168, 167, 153 (100%, $M^+ - C_7H_{15}$), 73 ($SiMe_3^+$); exact mass calcd for $C_{15}H_{28}OSi$ 252.1909, found 252.1909.

2-Methyl-4-furoic acid was prepared by similar desulfurization of a 2-(phenylthio)-5-methylfuran-3-carboxylic acid. It was sublimed at 100 °C (14 mm) and had mp 111.5–113.5 °C (lit.[5a] mp 114–115 °C): ^{1}H NMR ($CDCl_3$) δ 7.96 (s, 1 H, C5-H of furan), 6.40 (s, 1 H, C3-H of furan), 2.32 (s, 3 H, CH_3); IR (Nujol) 3150–2250, 1660, 1540, 1420, 1190, 1120, 950 cm^{-1}; mass spectrum, *m/e* 126 (100%, M^+), 109 ($M^+ - CH_3$), 43. Anal. Calcd for $C_6H_6O_3$: C, 57.19; H, 4.76. Found: C, 57.37; H, 4.76.

2-Methyl-4-(1-hydroxybutyl)furan was prepared as a colorless oil in the same manner from 2-(phenylthio)-3-(1-hydroxybutyl)-5-methylfuran: ^{1}H NMR ($CDCl_3$) δ 7.16 (s, 1 H, C5-H of furan), 5.93 (s, 1 H, C3-H of furan), 4.50 (t, J = 7 Hz, 1 H, CHOH), 2.20 (s, 3 H, $ArCH_3$), 1.61 (m, 2 H, $CH_2C_2H_5$), 1.25 (m, 2 H, CH_2CH_3), 0.90 (t, J = 7 Hz, CH_2CH_3); IR (Nujol) 3400, 2950, 1120, 1025, 920 cm^{-1}; mass spectrum, *m/e* 154 (M^+), 111 (100%, $M^+ - C_3H_7$), 93, 43; exact mass calcd for $C_9H_{14}O_2$ 154.0994, found 154.0994.

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Registry No. 1 (R^1 = CH_3), 534-22-5; 1 (R^1 = C_8H_{17}), 4179-38-8; 1 (R^1 = C_4H_9), 4466-24-4; 1 (R^1 = $CH(OC_2H_5)_2$), 13529-27-6; 1 (R^1 = H), 110-00-9; 2 (R^1 = C_4H_9), 77287-71-9; 2 (R^1 = CH_3), 77287-72-0; 2 (R^1 = C_8H_{17}), 77287-73-1; 2 (R^1 = $CH(OC_2H_5)_2$), 69197-87-1; 2 (R^1 = H), 16003-14-8; 3 (R^1 = C_4H_9), 77287-74-2; 3 (R^1 = CH_3), 77287-75-3; 3 (R^1 = C_8H_{17}), 77287-76-4; 4 (R^1 = C_4H_9; R^2 = C_8H_{17}), 77287-77-5; 4 (R^1 = C_4H_9; R^2 = CH_3), 77287-78-6; 4 (R^1 = CH_3; R^2 = $CH(OH)CH_2CH_2CH_3$), 77287-79-7; 4 (R^1 = CH_3; R^2 = $SiMe_3$), 77287-80-0; 4 (R^1 = C_8H_{17}; R^2 = $SiMe_3$), 77287-81-1; 4 (R^1 = CH_3; R^2 = CO_2H), 77287-82-2; 5 (R^1 = C_4H_9; R^2 = C_8H_{17}), 77287-83-3; 5 (R^1 = CH_3; R^2 = $SiMe_3$), 77287-84-4; 5 (R^1 = CH_3; R^2 = CO_2H), 21984-93-0; 5 (R^1 = CH_3; R^2 = $CH(OH)CH_2CH_2CH_3$), 77287-85-5; 5 (R^1 = C_8H_{17}; R^2 = $SiMe_3$), 77287-86-6; 1-iodooctane, 629-27-6; diphenyl disulfide, 882-33-7; trimethylsilyl chloride, 75-77-4; carbon dioxide, 124-38-9; methyl iodide, 74-88-4; butanal, 123-72-8.

Intramolecular Reactions of Reissert Compounds

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2-[*o*-(Chloromethyl)benzoyl]-1,2-dihydroisoquinaldonitrile (1) upon treatment with base yielded 5,6,13,14-didehydro-8-oxoberbine (3). 6,7-Dimethoxyisoquinoline gave 2-[*o*-(chloromethyl)benzoyl]-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile (4) which reacted with base to yield 2,3-dimethoxy-5,6,13,14-didehydro-8-oxoberbine (5). 2-(*o*-Formylbenzoyl)-1,2-dihydroisoquinaldonitrile (7) reacted with base to form phthalideisoquinoline (10).

Reissert compounds readily undergo base-catalyzed alkylation[1] and addition–rearrangement reactions with aldehydes.[2] Numerous examples of both types of reactions and their many applications in synthetic work have been

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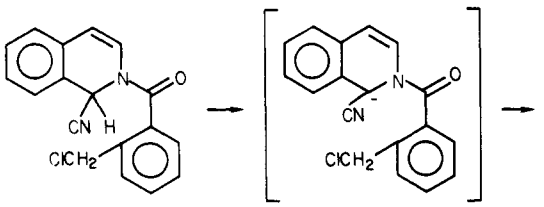
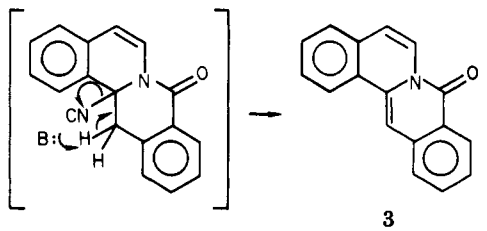
covered in review articles.[3-5] It seemed that a Reissert compound with a built in halomethyl or aldehyde group would undergo intramolecular reactions analogous to the intermolecular versions.

We decided to attempt first a synthesis of 2-(α-chloro-o-toluyl)-1,2-dihydroisoquinaldonitrile (1). This Reissert compound has the chloromethyl group present in a stragetic position, and we anticipated that an intramolecular displacement of the chloride in the anion 2 could be effected. With isoquinoline, potassium cyanide, and α-chloro-o-toluyl chloride[6] in a methylene chloride–water two-phase system,[7] the yield of 1 was found to be less than 20%. With a catalytic amount off benzyltriethylammonium chloride present, however, the desired product, 2, was obtained in 80% yield.



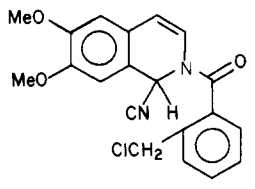
1 2



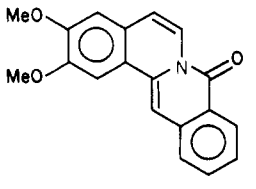
3

Cyclization of 1 required a base strong enough to remove the proton at the 1-position to form the anion 2 and hindered enough so that nucleophilic displacement of the external base on the chloromethyl group would not compete with formation of and subsequent cyclization of the Reissert anion. The use of lithium diisopropylamide in a mixture of tetrahydrofuran and hexamethylphosphoramide gave the cyclized product, 3, in 44% yield. Presumably the initial reaction involves intramolecular displacement of the chloride ion, with subsequent elimination of HCN.

Reaction of 6,7-dimethoxyisoquinoline with potassium cyanide, α-chloro-o-toluyl chloride, and a catalytic amount of benzyltriethylammonium chloride gave 2-(α-chloro-o-toluyl)-6,7-dimethoxyisoquinaldonitrile, 4, in 62% yield. Treatment of 4 with lithium diisopropylamide in hexamethylphosphoramide–tetrahydrofuran cosolvent afforded the cyclized compound, 5, in 74% yield.

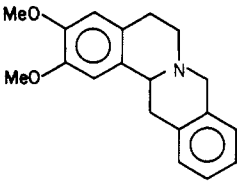


4



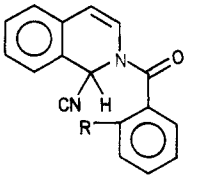
5

Compound 5 has been synthesized by an alternative route by Dyke et al.[8] When they treated this compound, first with lithium aluminum hydride, and subsequently with sodium borohydride, they obtained 2,3-dimethoxyberbine, 6, in 62% yield.



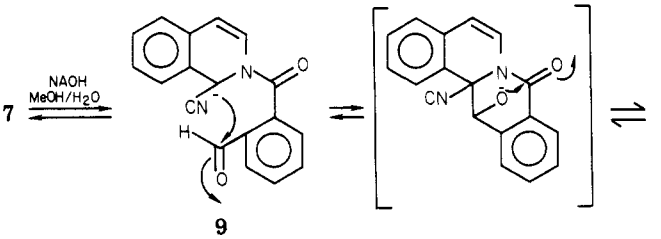
6

We next turned to a synthesis of 2-(o-formylbenzoyl)-1,2-dihydroisoquinaldonitrile, 7, which should undergo the characteristic reaction of a Reissert compound with an aldehyde in an intramolecular fashion. Oxidation of the bromomethyl isoquinaldonitrile 8 with Me_2SO–$AgBF_4$ in the presence of triethylamine by the method of Ganem and Boeckman[9] gave 7 in only 24% yield. One possible competing reaction is displacement of a molecule of dimethyl sulfoxide from an initially formed intermediate by triethylamine. Consequently, it was reasoned that the use of a hindered base would inhibit this side reaction. When the oxidation of 8 was repeated using diisopropylethylamine, the yield of 7 increased from 24% to 50%.

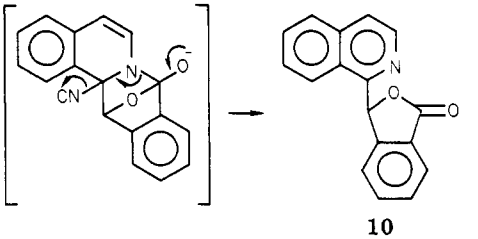


7, R = CHO
8, R = CH_2Br

We first used 50% NaOH in reaction with 7 according to the method of Jonczyk.[11] However, the yield of desired product 10 was quite low. Addition of a phase-transfer catalyst resulted in no improvement. However, when 7 was finally refluxed for 45 min with sodium hydroxide in aqueous methanol, phthalideisoquinoline, 10, was obtained in 58% yield, via the anion 9.



9



10

Phthalideisoquinoline, 10, was previously synthesized in 2% yield from isoquinoline N-oxide and methyl o-toluate.[12]

(1) Boekelheide, V.; Godfrey, J. C. *J. Am. Chem. Soc.* **1953**, *75*, 3679.
(2) Popp, F. D.; McEwen, W. E. *J. Am. Chem. Soc.* **1957**, *79*, 3773.
(3) McEwen, W. E.; Cobb, R. L. *Chem. Rev.* **1955**, *55*, 511.
(4) Popp, F. D. *Adv. Heterocycl. Chem.* **1968**, *9*, 1.
(5) Popp, F. D. *Adv. Heterocycl. Chem.* **1979**, *24*, 187.
(6) Burton, D. J.; Koppes, W. M. *J. Org. Chem.* **1975**, *40*, 3026.
(7) Popp, F. D.; Soto, A. *J. Chem. Soc.* **1963**, 1760.
(8) Brown, D. W.; Dyke, S. F.; Sainsbury, M.; Hardy, G. *J. Chem. Soc.* **1971**, 3219.
(9) Ganem, B.; Boeckman, R., Jr. *Tetrahedron Lett.* **1974**, 917.
(10) Pifferi, G.; Testa, E. *Tetrahedron* **1966**, *22*, 2107.
(11) Jonczyk, A. *Bull. Acad. Pol. Sci., Ser. Sci.* **1974**, *22*, 7.
(12) Natsume, M.; Tanabe, R. *Itsun Kenkyujo Nempo* **1968**, *15*, 21.

It is apparent that suitably substituted protoberberines, known alkaloids having potentially useful pharmacological properties, might conceivably be synthesized by use of Reissert compound as intermediates, but we have not yet succeeded in accomplishing this. Details of all of the work which we have carried out are available.[13]

Experimental Section

General Methods. All solvents used in this study were of reagent-grade quality and were dried by standard procedures. All melting points are uncorrected. Proton magnetic resonance spectra were taken on a Varian Model A-60 spectrophotometer, and the values are corrected for nonlinearity of the instrument used. The "usual workup procedure" consisted of washing the methylene chloride solution with water, 5% HCl, water, 5% NaOH, and water and then drying the solution over anhydrous magnesium sulfate prior to removal of the solvent in vacuo.

α-Chloro-*o*-toluyl Chloride. α-Chloro-*o*-toluyl chloride was prepared in 87% yield by the method of Burton and Koppes.[6]

2-[*o*-(Chloromethyl)benzoyl]-1,2-dihydroisoquinaldonitrile (1). A mixture of 2.4 mL (0.02 mol) of isoquinoline, 30 mL of methylene chloride, 6.5 g (0.1 mol) of potassium cyanide, 16 mL of water, and 176 mg (0.77 mmol) of benzyltriethylammonium chloride was stirred at 0 °C. To this mixture was added a solution of 7.34 g (0.039 mol) of α-chloro-*o*-toluyl chloride in 10 mL of methylene chloride over a period of 50 min. The mixture was stirred for an additional 10 min, and the layers were separated. The aqueous layer was washed with methylene chloride, and the combined organic layer, after the usual workup procedure, gave 6.85 g of dark red oil. Dry column chromatography on silica gel with chloroform as eluent afforded 5.6 g (93% crude yield) of a yellow oil. This, in turn, was chromatographed on silica gel with chloroform as eluent to yield 4.81 g (80%) of 1 as a tan solid. An analytical sample was prepared by several recrystallizations from benzene–Skelly C solvent to yield a white solid: mp 136–137 °C; IR (KBr) 1675 cm^{-1}; NMR ($CDCl_3$) δ 4.47 (d, 1, J = 12), 4.97 (d, 1, J = 12), 5.97 (d, 1, J = 12), 6.42 (d, 1, J = 7.2), 6.76 (s, 1), 7.05–7.70 (m, 8); mass spectrum, m/e 308, 155, 153 (base), 129.

Anal. Calcd for $C_{18}H_{13}N_2OCl$: C, 70.01; H, 4.24; N, 9.08. Found: C, 70.20; H, 4.37; N, 8.77.

5,6,13,14-Didehydro-8-oxoberbine (3). A solution of 2 mL (143 mmol) of anhdyrous diisopropylamine, 5.6 mL of 2.4 M (134 mmol) *n*-butyllithium/hexane, and 25 mL of anhdyrous tetrahydrofuran was stirred for 15 min at ambient temperature. This solution was then added over a period of 40 min to a stirred mixture of 2 g (65 mmol) of 1, 125 mL of anhydrous tetrahydrofuran, and 50 mL of hexamethylphosphoramide at −78 °C. The mixture was then allowed to warm slowly to room temperature. After 26 h, the reaction mixture was poured into 1.5 L of ice water, and the new mixture was filtered to yield 1.68 g of solid. Crystallization from methanol afforded 350 mg of a yellow solid, 3. Solvent was removed in vacuo from the filtrate, and dry column chromatography of the residue on silica gel with chloroform as eluent afforded an additional amount of the yellow solid, which, upon recrystallization from methanol, gave a total yield of 710 mg (44%) of 3: mp 144–146 °C; IR (KBr) 1655 cm^{-1}; NMR ($CDCl_3$) δ 6.58 (d, 1, J = 7.8), 7.15–7.70 (m, 7), 7.82–8.20 (m, 1), 8.33–8.65 (m, 2); mass spectrum, m/e 245 (base), 217, 216, 189; UV λ_{max} 256, 276, 287, 376, 392.[14]

Anal. Calcd for $C_{17}H_{11}NO$: C, 83.24; H, 4.52; N, 5.71. Found: C, 83.18; H, 4.52; N, 5.69.

6,7-Dimethoxyisoquinoline. 6,7-Dimethoxyisoquinoline was prepared in 38% yield by a known modification[15,16] of the Pomeranz–Fritsch reaction.

2-[*o*-(Chloromethyl)benzoyl]-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile (4). A mixture of 3.78 g (0.02 mol) of 6,7-dimethoxyisoquinoline, 30 mL of methylene chloride, 6.5 g (0.1 mol) of potassium cyanide, 16 mL of water, and 176 mg (0.77 mmol) of benzyltriethylammonium chloride was stirred at 0 °C. To this mixture was added a solution of 7.52 g (0.04 mol) of α-chloro-*o*-toluyl chloride in 10 mL of methylene chloride over a period of 50 min. The mixture was stirred for an additional 10 min, and the layers were separated. The aqueous layer was washed with methylene chloride, and the combined organic solution, after the usual workup procedure, gave 7.0 g of a brick-red solid. Dry column chromatography on silica gel with chloroform as eluent afforded 4.6 g (62.3% crude yield) of a solid, which was recrystallized from benzene to give 2.90 g (39%) of 4 as a white powder: mp 179 °C dec; IR (KBr) 1665 cm^{-1}; NMR ($CDCl_3$) δ 3.91 (s, 6), 4.48 (d, 1, J = 12), 4.93 (d, 1, J = 12), 5.92 (d, 1, J = 7.2), 6.32 (d, 1, J = 7.2), 6.50–7.05 (m, 3), 7.13–7.75 (m, 4); mass spectrum, m/e 368, 333, 189 (base).

Anal. Calcd for $C_{20}H_{17}N_2O_3Cl$: C, 65.13; H, 4.65; N, 7.60. Found: C, 65.07; H, 4.54; N, 7.62.

2,3-Dimethoxy-5,6,13,14-didehydro-8-oxoberbine (5). A solution of 1.2 mL (86 mmol) of dry diisopropylamine, 3.4 mL (82 mmol) of 2.4 M *n*-butyllithium/hexane, and 10 mL of anhydrous tetrahydrofuran was stirred for 15 min at ambient temperature. This solution was then added over a period of 1 h to a stirred mixture of 2.0 g (54 mmol) of 4, 125 mL of anhydrous tetrahydrofuran, and 50 mL of hexamethylphosphoramide at −78 °C. After the addition, the mixture was allowed to warm slowly to room temperature. After 21 h, the reaction mixture was poured into 2 L of ice–water, and the new mixture was filtered to give a yellow-brown solid, which, upon recrystallization from methanol/water, yielded 986 mg of yellow needles (74%) of 5: mp 233–234 °C (lit.[8] mp 230–231 °C); IR 1660, 1615 cm^{-1} (lit.[8] IR 1660, 1615 cm^{-1}); NMR ($CDCl_3$) δ 3.95 (s, 3), 4.02 (s, 3), 6.63 (d, 1, J = 8.4), 6.78 (s, 1), 7.14 (s, 1), 7.24–7.76 (m, 4), 8.42–8.70 (m, 2); mass spectrum, m/e 305 (base), 261, 152.5; UV λ_{max} 253, 269, 279, 291, 390.

Anal. Calcd for $C_{19}H_{15}NO_3$: C, 74.74; H, 4.95; N. 4.59. Found: C, 74.94; H, 5.03; N, 4.60.

α-Bromo-*o*-toluic Acid. α-Bromo-*o*-toluic acid was prepared in 64% yield from phthalide by the method of Pifferi and Testa.[10]

α-Bromo-*o*-toluyl Chloride. α-Bromo-*o*-toluyl chloride was prepared in 90% yield by the method of Pifferi and Testa.[10]

2-[*o*-(Bromomethyl)benzoyl]-1,2-dihydroisoquinaldonitrile (8). A mixture of 4.8 mL (0.041 mol) of isoquinoline, 50 mL of methylene chloride, 13 g (0.2 mol) of potassium cyanide, 32 mL of water, and 350 mg (1.5 mmol) of benzyltriethylammonium chloride was stirred at 0 °C. To this mixture was added a solution of 14.5 g (0.062 mol) of α-bromo-*o*-toluyl chloride in 30 mL of methylene chloride over a period of 50 min. The mixture was stirred for an additional 10 min, and the layers were separated. The aqueous layer was washed with methylene chloride, and the combined organic layer, after the usual workup procedure, gave 12 g (86% crude yield) of a gold solid. Dry column chromatography on silica gel with chloroform as eluent afforded 8.8 g (61%) of 8. An analytical sample was prepared by several recrystallizations of the crude solid from ethanol. A white solid was obtained: mp 134–135 °C; IR (KBr) 1677 cm^{-1}; NMR ($CDCl_3$) δ 4.38 (d, 1, J = 10.8), 4.92 (d, 1, J = 10.8), 6.00 (d, 1, J = 7.8), 6.42 (d, 1, J = 7.8), 6.74 (s, 1), 7.10–7.80 (m, 8); mass spectrum, m/e 354, 352, 199, 197 (base), 129.

Anal. Calcd for $C_{18}H_{13}N_2OBr$: C, 61.20; H, 3.71; N, 7.93; Br, 22.62. Found: C, 61.37; H, 3.84; N, 7.93; Br, 22.85.

2-(*o*-Formylbenzoyl)-1,2-dihydroisoquinaldonitrile (7). A solution of 7 g (0.036 mol) of anhydrous silver tetrafluoroborate in 35 mL of anhydrous dimethyl sulfoxide was protected from light and stirred at ambient temperature under nitrogen. To this solution was added 6 g (0.017 mol) of 8. After the mixture had been stirred for 39 h, 3.5 mL (0.02 mol) of *N,N*-diisopropylethylamine was added. After 15 min, the mixture was poured into 300 g of ice–water and filtered. The residue was extracted with methylene chloride. The methylene chloride solution was dried with anhydrous magnesium sulfate, and the solvent removed in vacuo to yield 5 g of a white, amorphous solid. This was crystallized from methanol/water to yield 2.43 g (50%) of white crystals of 7. An analytical sample was prepared by several recrystallizations from methanol/water: mp 163–164 °C; IR (KBr)

(13) Tyrell, J. A., III Ph.D. Dissertation, University of Massachusetts, Amherst, MA, 1978; *Diss. Abstr. Int. B.* **1978**, *39*(5), 2318; *Chem. Abstr.* **1979**, *90*, 72034.

(14) Cf.: Ruchirawat, S.; Lertwanawatana, W.; Thepchumrune, P. *Tetrahedron Lett.* **1980**, 189.

(15) Birch, A. J.; Jackson, A. H.; Shannon, P. V. R. *Tetrahedron Lett.* **1972**, *4789*.

(16) Coomes, R. M.; Falck, J. R.; Williams, D. K.; Stermitz, F. R. *J. Org. Chem.* **1973**, *38*, 370.

1693, 1671 cm^{-1}; NMR ($CDCl_3$) δ 5.95 (d, 1, J = 7.2), 6.25 (d, 1, J = 7.2), 6.85 (s, 1), 7.05–8.13 (m, 8), 10.05 (s, 1); mass spectrum, m/e 288, 133 (base), 129.

Anal. Calcd for $C_{18}H_{12}N_2O_2$: C, 74.98; H, 4.20; N, 9.72. Found: C, 74.88; H, 4.21; N, 9.95.

Phthalideisoquinoline (10) from 7. To a refluxing solution of 0.50 g (1.7 mmol) of **7** in 50 mL of methanol was added 4 mL (0.01 mol) of 10% aqueous NaOH. The solution was refluxed for 45 min, solvent removed in vacuo, and the residue dissolved in 50 mL of water. This solution was poured into a solution of 10 g of ammonium chloride in 50 mL of water. The resulting solution was made strongly acidic with 10% HCl, boiled, cooled, and filtered. The filtrate was made weakly alkaline with 10% NaOH solution, cooled, and scratched to afford 260 mg (58%) of **10** as a white solid. An analytical sample was prepared by several recrystallizations from 95% ethanol: mp 168–169 °C dec (lit.[12] mp 150–152 °C); IR (KBr) 1770 cm^{-1} (lit.[12] IR 1770 cm^{-1}); NMR ($CDCl_3$) δ 7.22 (s, 1), 7.40–8.60 (m, 10); mass spectrum, m/e 261, 232 (base), 133, 128.

Anal. Calcd for $C_{17}H_{11}NO_2$: C, 78.14; H, 4.23; N, 5.36. Found: C, 78.07; H, 4.46; N, 5.24.

1-(*o*-Carbomethoxybenzyl)isoquinoline 2-Oxide. The preparation of 1-(*o*-carbomethoxybenzyl)isoquinoline 2-oxide was carried out by the method of Natsume and Tanabe.[12]

Phthalideisoquinoline (10). An independent synthesis of phthalideisoquinoline (**10**) was effected by the method of Natsume and Tanabe.[12] A solution of 90 mg of 1-(*o*-carbomethoxybenzyl)isoquinoline 2-oxide dissolved in 3 mL of acetic anhydride was refluxed for 3 h and evaporated to dryness under reduced pressure, and the resulting black oil dissolved in 10 mL of methanolic HCl prepared from 0.5 mL of concentrated HCl and 9.5 mL of methanol. The solution was refluxed for 1 h and evaporated in vacuo, and 30 mL of water added. The mixture was filtered and 5 g of ammonium chloride added to the filtrate. The filtrate was made weakly alkaline with 10% sodium hydroxide solution, and 0.1 g of phthalideisoquinoline (**10**) precipitated as an amorphous tan solid; mp 168–169 °C; mp 168–169 °C in admixture with the sample prepared from **7**. IR and NMR spectra of the two samples were identical.

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Synthesis and Reactions of Deuterated 2-(Alkylimino)-3-nitrosooxazolidines, 3-Alkyl-1-(2-hydroxyethyl)-1-nitrosoureas, and Related Compounds as Possible Intermediates in the Aqueous Decomposition of 3-Alkyl-1-(2-chloroethyl)-1-nitrosoureas[1a]

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Decomposition of CCNU-α-d_2 (**7**) in pH 7.2 phosphate buffer or of CINO-α-d_2 (**9**) or CHNU-α-d_2 (**8**) with the addition of chloride ion gives rise to the same spectrum of products, including deuterium-free acetaldehyde (**29**), a mixture of the two deuterio-2-chloroethanols, 2-hydroxy-2,2-dideuterioethyl cyclohexyl carbamates, and vinyl chloride containing one deuterium (i.e., opposite the results obtained in the corresponding reaction of BCNU-α-d_4). The products were identified and the number and position of the deuterium labels determined by GC/MS. The results are interpreted in terms of two decomposition pathways for CCNU. The first decomposition pathway operating for CCNU is via an intermediate 2-chloroethanediazohydroxide or the equivalent 2-chloroethyl cation in agreement with the results of other workers. The second pathway may involve reversible conversion of CCNU-α-d_2 (**7**) to CINO-α-d_2 (**9**) and then ring opening of the latter to CHNU-α-d_2 (**8**). Independent decomposition of **8** provides evidence for its conversion to a 1,1-dideuterio-2-hydroxyethanediazohydroxide (**41**) leading to the isolated carbamates **36** and **44**. The intermediacy of species **41** may account for the formation of 2-hydroxyethylated nucleosides observed when (2-chloroethyl)nitrosoureas react with DNA. An alternative ring-opening reaction of **9** leads to a 2-hydroxydiazoethyl cyclohexylcarbamate species (**37**), elimination of which and attack by halide ion may account for the vinyl halide species formed. Further evidence in support of these competing pathways employing additional specifically deuterated intermediates is described and discussed.

(2-Haloethyl)nitrosoureas including 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU), 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU), and others are of clinical value in the treatment of a range of neoplasms.[1-5] These compounds decompose readily under physiological conditions and have been found to alkylate and cross-link DNA both in vivo and in vitro.[6-9] Studies on the nature

(1) (a) Abbreviations are as follows: CCNU-α-d_2, 3-cyclohexyl-1-nitroso-1-(1,1-dideuterio-2-chloroethyl)urea; CCNU-β-d_2, 3-cyclohexyl-1-nitroso-1-(2,2-dideuterio-2-chloroethyl)urea; CHNU-α-d_2, 3-cyclohexyl-1-nitroso-1-(1,1-dideuterio-2-hydroxyethyl)urea; CHNU-β-d_2, 3-cyclohexyl-1-nitroso-1-(2,2-dideuterio-2-hydroxyethyl)urea; CINO-α-d_2, 2-(cyclohexylimino)-3-nitroso-4,4-dideuteriooxazolidine; CINO-β-d_2, 2-(cyclohexylimino)-3-nitroso-5,5-dideuteriooxazolidine; BCNU-α-d_4, bis(1,1-dideuterio-2-chloroethyl)-*N*-nitrosourea. (b) S. K. Carter, F. A. Schabel, L. E. Broder, and T. P. Johnson, *Adv. Cancer Res.*, **16**, 273 (1972).
(2) G. D. Wheeler ACS *Symp. Ser.*, **No. 30**, 87–119 (1976).
(3) V. A. Levin and C. B. Wilson, *Cancer Treat. Rep.*, **60**, 719 (1976).
(4) J. A. Montgomery, *Cancer Treat. Rep.*, **60**, 651 (1976).
(5) V. DeVita, P. Carbone, A. Owens, G. L. Gold, M. J. Krant, and J. Edmonson, *Cancer Res.*, **25**, 1876 (1965).
(6) K. W. Kohn, *Cancer Res.*, **37**, 1450 (1977).
(7) D. B. Ludlum, B. S. Kramer, J. Wang, and C. Fenselau, *Biochemistry*, **14**, 5480 (1975).
(8) M. Colvin, R. B. Brundrett, W. Cowens, I. Jardine, and D. B. Ludlum, *Biochem. Pharmacol.*, **25**, 695 (1976).
(9) J. W. Lown, L. W. McLaughlin, and Y. M. Chang, *Bioorg. Chem.*, **7**, 97 (1978).

0022-3263/81/1946-2479$01.25/0