phthalate, mp 85–87 °C, and dimethyl 3-hydroxy-5-(phenylthio)-o-phthalate, mp 75–77 °C, in 2:1 ratio with 80% yield.

Compound **16**: IR (KBr): 2952, 1740, 1725, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.73 (s, 3 H), 3.82 (s, 3 H), 3.9 (s, 3 H), 6.93 (d, J = 2 Hz, 1 H), 7.33 (s, 5 H), 7.45 (d, J = 2 Hz, 1 H); MS, m/e (relative intensity) 332 (M^+, 69) 301 (100), 286 (13), 269 (18), 241 (19), 171 (17), 134 (18); exact mass calcd for $C_{17}H_{16}O_5S$ 332.072, obsd 332.067.

Compound **17**: IR (KBr) 2960, 1732, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.8 (s, 3 H), 3.83 (s, 3 H), 6.47 (s, 2 H), 7.38 (m, 5 H), 10.63 (s, 1 H); MS, m/e (relative intensity) 318 (M^+, 5), 252 (29), 208 (33), 177 (30), 149 (49), 134 (34), 28 (100); exact mass calcd for $C_{16}H_{14}O_5S$ 318.055, obsd 318.056.

Dimethyl (Z)-3-(Phenylthio)-5-(methoxycarbonyl)-2-adepate (18). To a well-stirred solution of **3b** (1.12 g, 4 mmol) and dimethyl maleate (0.5 mL, 4 mmol) in 20 mL of CH_2Cl_2 under nitrogen at −78 °C was added titanium tetrachloride (0.45 mL, 4 mmol). After 5 h, the dark red colored mixture was added to aqueous $NaHCO_3$ and extracted with ether. The extract was dried (Na_2SO_4) and evaporated to give an oil, which was column chromatographed (eluant, 25% ethyl acetate–hexane) to give 18 as an oil in 78% yield. The E isomer of 18 was also formed as a minor product, as evidenced by ^1H NMR.

Compound **18**: IR (film) 2950, 1745, 1730, 1705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.13 (m, 5 H), 5.75 (s, 1 H), 3.63 (s, 3 H), 3.50 (s, 3 H), 3.43 (s, 3 H), 2.03–2.83 (m, 5 H); MS, m/e (relative intensity) 352 (M^+, 27), 320 (25), 289 (24), 261 (38), 183 (50), 28 (100); exact mass calcd for $C_{17}H_{20}O_6S$ 352.098, obsd 352.098.

Acknowledgment. Financial support from NSERC and FCAC are gratefully acknowledged. C.V.C.P. thanks McGill University for the award of the Bindra Fellowship.

Registry No. **3a**, 102736-24-3; **3b**, 102736-25-4; (*E*)-**5a**, 102736-26-5; (*E*)-**5b**, 102736-27-6; **6a**, 102736-28-7; **6b**, 102736-29-8; **6c**, 102736-30-1; **6d**, 102736-31-2; (*E*)-**6e**, 102736-32-3; (*Z*)-**6e**, 102736-33-4; **8** (R = Ph), 102736-34-5; **10a**, 102736-35-6; **10b**, 102736-36-7; **11**, 74590-75-3; **12**, 102736-37-8; **13**, 102736-38-9; **14**, 102736-39-0; **15**, 23194-33-4; **16**, 102736-40-3; **17**, 102736-41-4; (*Z*)-**18**, 102736-42-5; (*E*)-**18**, 102736-43-6; (*E*)-3-(benzylthio)crotonic acid, 67959-54-0; benzaldehyde, 100-52-7; acetone, 67-64-1; cyclohexanone, 108-94-1; 4-(phenylthio)-1-oxaspiro[5.5]undec-3-en-2-one, 102736-44-7; 4-(trimethylsiloxy)-pent-3-en-2-one, 13257-81-3; cyclohexanone trimethylsilyl enol ether, 6651-36-1; dimethyl acetylenedicarboxylate, 762-42-5; dimethyl maleate, 624-48-6.

Nucleophilic Aromatic Substitution with Elimination in a Dinitrosalicylic Lactone or Ester via Meisenheimer Intermediates

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The dinitro lactone **1b** and dinitro ester **2b** derived from salicylic acid undergo S_NAr reactions in the presence of a variety of N-, O-, and S-nucleophiles. Substitution is accompanied by elimination of the β-ethyleneoxy group, the ester group in no case being retained in the product. The dinitro amide **3b** was inert under the same conditions. With amines as nucleophiles, the final products are salicylamides; with aniline, hydroxide, methoxide, and thiophenolate/methanol, salicylates are formed. Thiocyanate effected S_N2 cleavage of the ether in **1b** or **2b**. Meisenheimer intermediates A and B could be isolated and characterized and were shown to be interconvertible. They, in turn, can be transformed to the final S_NAr products with the appropriate nucleophiles.

In the course of exploring the chemistry of salicylate derivatives, the dinitro lactone **1b** was subjected to treatment with aqueous ammonia, with the intention of converting it to the salicylamide **3b**. The unexpected result was formation of "iramine" (**4c**; Table I), a potent anticoccidiosis agent.[2]

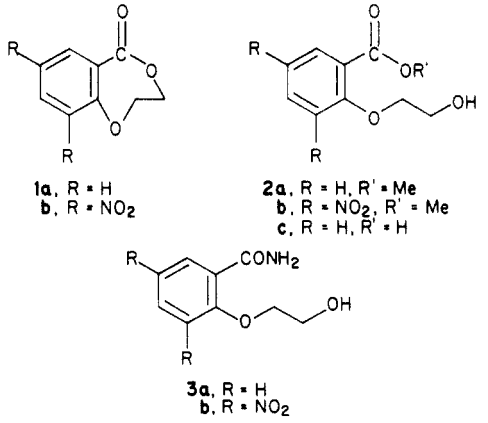
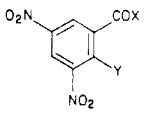


Table I. S_NAr Products from Lactone 1b or Ester 2b with Various Nucleophiles

nucleophile	product	X	Y
	 4		
NaOH	**4a**	OH[a]	OH
PhSH, NaOH	**4b**	OH[a]	SPh
NH_3	**4c**	NH_2	NH_2
NH_2CH_3	**4d**	$NHCH_3$	$NHCH_3$
$NH(CH_3)_2$	**4e**	$N(CH_3)_2$	$N(CH_3)_2$
$PhNH_2$[c]	**4f**	OH[b]	NHPh
CH_3O^-Na	**4g**	OH[a]	OCH_3

[a] Usually first isolated as Na salt. [b] First isolated as anilinium salt. [c] Lactone substrate only.

Because the transformation of **1b** to iramine involves ammonolysis of the lactone as well as nucleophilic displacement of the alkoxy group ortho and para to the nitro substituents, we were interested in determining whether the dual-step behavior was unusual for ammonia as a nucleophile and, further, which step was occurring first. We therefore undertook a systematic study of the behavior of **1b** and related compounds toward a series of nucleophiles (Nu). Among the reagents chosen for study were several N-, O-, and S-nucleophiles known to be effective in S_NAr

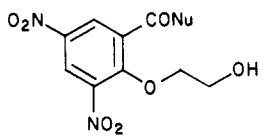
(1) Taken in part from: Rothenberger, S. D. Ph.D. Dissertation, University of New Hampshire, 1985.

(2) (a) Koblova, I. A.; Shmulevich, A. I.; Piskov, V. B. *Tr. Gos. Nauchno-Kontrol'n. Inst. Vet. Prep.* **1969**, *15*, 316; *Chem. Abstr.* **1971**, *77*, 57116m. (b) Koblova, I. A.; Kuzin, A. G. *Tr. Gos. Nauchno-Kontrol'n. Inst. Vet. Prep.* **1971**, *17*, 319; *Chem. Abstr.* **1971**, *77*, 15513h. (c) Koblova, I. A.; Piskov, V. G. *Khim. Sel'sk. Khoz.* **1973**, *11*, 551; *Chem. Abstr.* **1973**, *79*, 111588y.

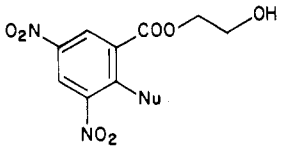
0022-3263/86/1951-3016$01.50/0

reactions.[3] We found that the nucleophilic substitution was indeed quite general, in spite of the relatively poor leaving group ability of alkoxy in such reactions. The structures of products from **1b** and **2b** with the various nucleophiles are summarized in Table I.

The striking characteristic of all the nucleophilic substitution reactions is that the β-hydroxyethoxy group is lost. That is, products of types **5** and **6** were never observed. The facile hydrolysis of β-hydroxy ester **6** or its conjugate base is consistent with the anchimeric assistance in hydrolysis of ethylene glycol monoesters and other similarly constituted esters.[4] In the case where ammonia



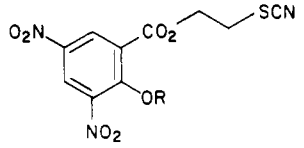
5



6

or aliphatic amines are nucleophiles, the products **4c–4e** are amides. In other cases the carboxylates are formed, and these were converted to the free carboxylic acids **4a,b,f,g** by acidification. Final products were either already reported in the literature (e.g., iramine) or were prepared independently from 2-chloro-3,5-dinitrobenzoic acid and the appropriate nucleophile [e.g., 2-(phenylthio)-3,5-dinitrobenzoic acid (**4b**)]. The dinitro ester **2b**, prepared independently by methanolysis of **1b**, also led to S_NAr products with loss of the β-hydroxyethoxy group. This was confirmed for every nucleophile in Table I except aniline. The fact that the dinitro amide **3b** was unchanged under ammonolysis conditions suggests that the S_NAr reaction precedes amide formation in the multistep pathway leading to **4c**.

The results with thiocyanate nucleophile warrant special attention. It failed to react with dinitro lactone **1b** when the latter was heated with KSCN or NH_4SCN in THF, ethanol, water, or mixtures of the latter two solvents under a variety of conditions. This feeble nucleophilicity of SCN in S_NAr reactions has been documented.[5] It was found, however, that brief treatment of **1b** with $KSCN/Me_2SO$ under nitrogen at 120 °C afforded, after aqueous workup, a salt **7a**, which was fully characterized by IR, ^{1}NMR, ^{13}C NMR, UV–vis, and elemental analysis. Acidification of the salt gave the phenolic thiocyanatoethyl ester **7b**, which was characterized in the same way.

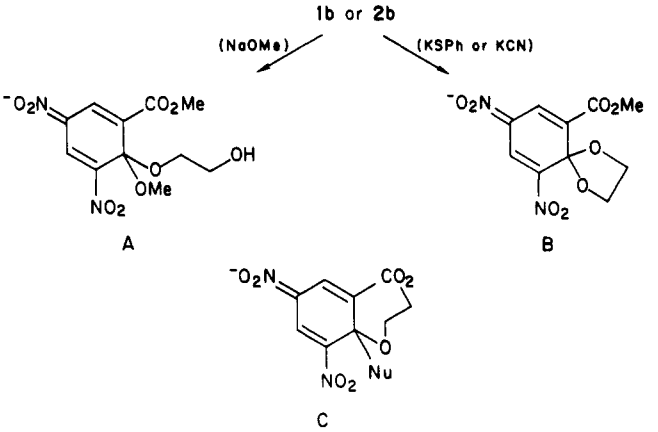


7a, R = K
b, R = H

This facile S_N2 cleavage of the phenolic ether appeared promising as a mild synthetic method and so was explored with other substrates. It was found that other dinitro phenolic ethers were cleaved smoothly under the same conditions. 2,4-Dinitroanisole, 2-methoxy-3,5-dinitrobenzoic acid, methyl 2-methoxy-3,5-dinitrobenzoate, and **2b** afforded the corresponding phenols in 98%, 93%, 92%, and 92% yields, respectively. *o*- and *p*-nitroanisoles and 1,2-(methylenedioxy)-4-nitrobenzene were recovered unchanged. Although $KSCN/Me_2SO$ appears to be useful only for activated phenols, the reaction is rapid and easily carried out. Cleavage with $NaCN/Me_2SO$[6] requires higher temperatures and reaction times of up to 2 days. The fact that esters are unaffected by the reagent constitutes an advantage over boron reagents, which often cleave esters as well as ethers.[7]

To our knowledge this is the first observation of the chemoselectivity by thiocyanate in nitrated substrates susceptible to both S_NAr and S_N2 attack.

We have succeeded in isolating and characterizing two different Meisenheimer intermediate salts A and B from **1b** or **2b** by using 1 equiv of nucleophile and interrupting the reactions after brief periods at room temperature. A, the "mixed" Meisenheimer complex, was formed from either substrate with NaOMe and identified as the Na salt.



A B C

The "spiro" Meisenheimer complex B, as its K salt, came from either **1b** or **2b** and 1 equiv of K thiophenolate or KCN in MeOH. In no case were we able to isolate the bicyclo Meisenheimer complex C, which would have formed by nucleophile attack on **1b** without subsequent ring opening.

The salts A and B were characterized by elemental analysis and UV, IR, ^{1}H NMR, ^{13}C NMR, and MS spectroscopy. The UV spectra of A and B are highly characteristic of diene chromophores in Meisenheimer complexes, with maxima at 388 and 475 nm. Moreover, the extinctions at these positions are greatly enhanced by the addition of traces of base, behavior that has been observed repeatedly in the past.[3c,8,9] The IR spectra of A and B are similar but distinctive in the fingerprint regions. The ^{1}H and ^{13}C NMR spectra are suprisingly similar. In fact, the ^{1}H and ^{13}C NMR spectra taken of A in Me_2SO amounted to a composite of the corresponding spectra of B and of

(3) For some of the more recent reviews of nucleophilic aromatic substitution, see: (a) "Nucleophilic Aromatic Substitution" *Organic Reaction Mechanisms*; Wiley: New York, 1965–1984; Chapter 7. (b) "Nucleophilic Substitution" *Aromatic and Heteraromatic Chemistry*; Specialist Periodical Reports; The Chemical Society: London, 1973; Vol. 1, Chapter 8. (c) Foster, R.; Fyfe, C.A. *Rev. Pure Appl. Chem.* **1966**, *16*, 61. (d) Buncel, E.; Norris, A. R.; Russell, K. E. *Q. Rev. Chem. Soc.* **1968**, *22*, 123. (e) Crampton, M. R. *Adv. Phys. Org. Chem.* **1969**, *7*, 211. (f) Strauss, M. J. *Acc. Chem. Res.* **1974**, *7*, 181. (g) Jorgensen, W. L.; Pieshoff, C. E. *J. Org. Chem.* **1985**, *50*, 1056. (h) Buncel, E.; Crampton, M. R.; Strauss, M. J.; Terrier, F. *Studies in Organic Chemistry*; Elsevier Science: New York, 1984; Vol. 14.

(4) Balakrishnan, M.; Rao, G. V.; Venkatasubramanian, N. *J. Chem. Soc., Perkin Trans. 2* **1974**, 6; *Aust. J. Chem.* **1974**, *27*, 2325 and references cited therein.

(5) Miller, J.; *Aust. J. Chem.* **1956**, *9*, 74, 304. Miller, J.; Parker, A. J.; Bolto, B. A. *J. Am. Chem. Soc.* **1957**, *79*, 93; Miller, J.; Wong, K. W. *Aust. J. Chem.* **1965**, *18*, 117; *J. Chem. Soc.* **1965**, 5454.

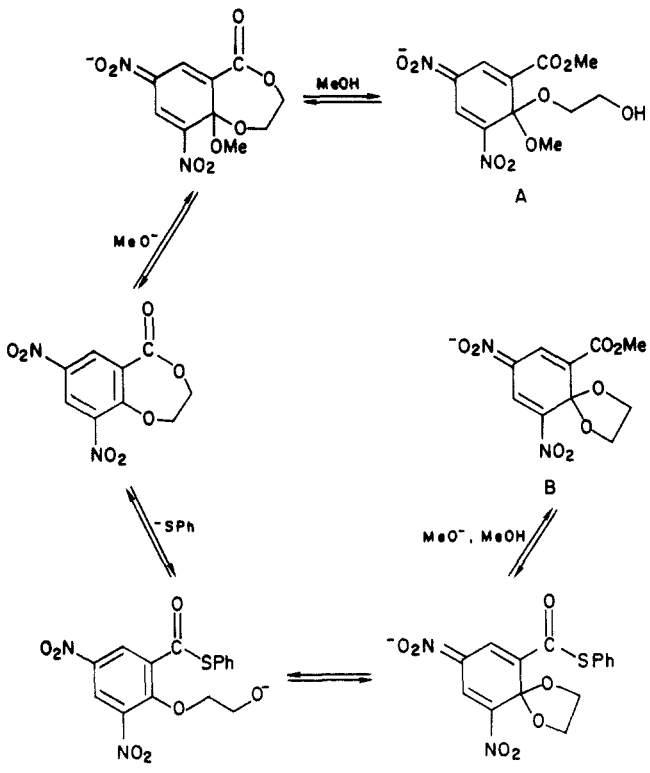
(6) McCarthy, J. R.; Moore, J. L.; Gregge, R. J. *Tetrahedron Lett.* **1978**, 5183.

(7) For examples of ester cleavage with boron reagents, see: Frazen, M. J.; Gerrard, W. *J. Chem. Soc.* **1955**, 2959. Manchand, P. S. *J. Chem. Soc., Chem. Commun.* **1971**, 667. Felix, A. M. *J. Org. Chem.* **1974**, *39*, 1427. Yazawa, H.; Tanaka, K.; Kariyone, K. *Tetrahedron Lett.* **1974**, 3995. Smith, K. M.; Langy, K. C. *J. Chem. Soc., Chem. Commun.* **1981**, 283. Niwa, H.; Hida, T.; Yamada, K.; *Tetrahedron Lett.* **1981**, *22*, 4239.

(8) Strauss, M. J. *Chem. Rev.* **1970**, *70*, 667.

(9) Terrier, F. *Chem. Rev.* **1982**, *82*, 77.

Scheme I



methanol. Our explanation is that the mixed Meisenheimer A in solution is rapidly transformed to B with loss of methanol. In a control experiment we could demonstrate this conversion of A to B simply by dissolving A in acetone and reisolating the material (see Experimental Section). The equivalency of the two CH_2 groups in B, apparent in both ^1H and ^{13}C NMR spectra, is attributed to the rapid opening and closing of the spiro ring. A similar observation in the ^1H NMR spectrum of a spiro Meisenheimer complex was reported earlier.[10]

The formation of B is of particular interest because it cannot result from a simple nucleophilic addition to the substrate as is the case in the formation of A. A possible route to B involves initial nucleophilic addition to the carbonyl (rather than at the activated arene carbon), followed by ring opening to generate the alkoxide, which then adds at the arene carbon. Consistent with this explanation is the nature of the nucleophiles that led to B. Thiophenoxide is generally considered a weaker nucleophile than methoxide;[8,11,12] cyanide has long been recognized as a reagent leading to unexpected products with activated aryl halides.[13] Methoxide, on the other hand, a good S_NAr nucleophile, is effective in generating the mixed Meisenheimer complex A, which would result from its attack on the aromatic ring. These steps in the formation of A and B are illustrated for the dinitro lactone **1b** with methoxide and thiophenoxide in Scheme I. Formation of B is also consistent with the recent finding of Bernasconi and Howard[14] that spiro Meisenheimer complexes form and decompose much faster than dimethoxy complexes, the latter being analogous to our intermediate A.

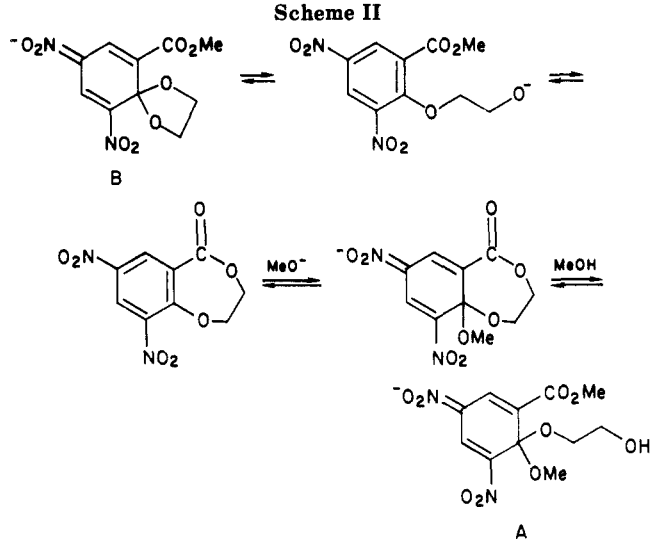
(10) Fyfe, C. A. *Tetrahedron Lett.* **1968**, 659.
(11) Crampton, M. R.; *J. Chem. Soc. B* **1968**, 1208.
(12) Bartoli, G.; Di Nunno, L.; Forlani, L.; Todesco, P. E. *Int. J. Sulfur Chem. Part C* **1971**, *6*, 77.
(13) Bunnett, J. F.; Zahler, R. E. *Chem. Rev.* **1949**, *49*, 273.
(14) Bernasconi, C. F.; Howard, K. A. *J. Am. Chem. Soc.* **1982**, *104*, 7248–7257 and references cited therein.

Table II. Products from Meisenheimer Intermediates A or B

Meisenheimer intermed	product	yield, %	Meisenheimer intermed	product	yield, %
A	**2b**	90	A	**4c**	85
B	**2b**	90	B	**4c**	94
A	**4a**	95	B	**4e**	90
B	**4a**	93	A	**4g**	84
A	**4b**	85	B	**4g**	87[a]
B	**4b**	95			

[a] First converted to A; yield based on material remaining after removal of a 1-mL aliquot.

Scheme II



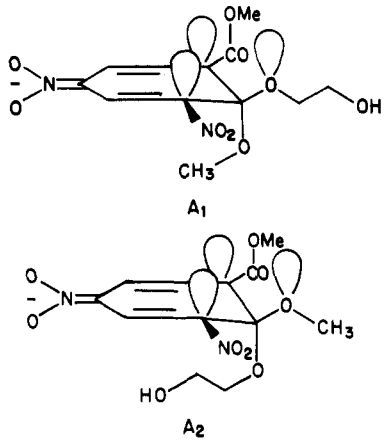
Both Meisenheimer complexes could be converted further to the observed final products of S_NAr displacement by *heating* them with the appropriate nucleophiles (see Table I and Experimental Section). The results of these experiments are summarized in Table II.

Much to our surprise, the two Meisenheimer intermediates have been shown to be interconvertible. B is converted to A with methoxide/methanol, while A is converted to B with thiophenoxide/methanol. Formation of B from A follows from Scheme I, if it is assumed that all steps are readily reversible; in the absence of methoxide and presence of thiophenoxide, the favored product is B. Interconversion of B to A with methoxide can occur through a similar set of equilibria, as represented in Scheme II. A similar set of steps can be written for the interconversion from the ester **2b**. Our attempts to follow the interconversion of A and B by NMR spectroscopy were thwarted by the rapid conversion of A to B in acetone or Me_2SO solvents.

The decomposition of A via lactone **1b** or ester **2b** requires that methoxide is eliminated rather than the β-hydroxyethoxy group. In support of this pathway, we could demonstrate in separate experiments that brief treatment of A (as well as B) with dilute HCl gave the ester **2b** and not methyl 2-methoxy-3,5-dinitrobenzoate (see Table II). Preferential elimination of methoxy rather than β-hydroxyethoxy from A provides one more example in support of Deslongchamps' hypothesis of stereoelectronic control.[15] The Meisenheimer intermediate A can be arranged in two conformations A_1 and A_2 such that the p orbitals at the 2- and 6-positions of the ring are antiperiplanar to the C–O bond being broken (Scheme III). In the former the methoxy group is ideally aligned for de-

(15) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: New York, 1985.

Scheme III



parture; in the latter the β-hydroxyethoxy group. (A similar representation for transiton states of spiro and dimethoxy Meisenheimer intermediates has been depicted by Bernasconi and Howard[14]). Although the barriers to rotation about the C–O bonds of the methoxy and β-hydroxyethoxy are presumably low, several conformations resulting from rotations about these bonds are unfavorable because of anomeric effects, exo-anomeric effects,[16] or the presence of large substituents at the 2- and 6-positions. The conformations in Scheme II, with the departing groups "under" the diene portion of the structure, are relatively free of these unfavorable effects; but A_1, with the smaller methoxy group in this crowded environment, is preferred over the arrangement in A_2. If indeed these two conformers are substantially populated, the former would lead preferentially to the products, which are, in fact observed—those resulting from loss of methoxide, with formation of the spirocyclic intermediate and **2b**. Although Bernasconi and Howard have already used stereoelectronic control convincingly to rationalize the facile opening of a spirocyclic Meisenheimer intermediate, its application as in Scheme III could serve to explain not only our results but also the preferential loss of phenoxide over methoxide in the elusive 1-methoxy-1-phenoxy Meisenheimer intermediate.[17]

The effective use of a broad range of nucleophiles to carry out the S_NAr reactions described in the present work not only has interesting mechanistic implications but offers promise for synthetic purposes. Thiophenoxide attack leads to derivatives of nitrated thiosalicylic acid, compounds not particularly readily available from other sources. The general efficacy of amine nucleophiles allows entry into the nitrated anthranilic acid series.

Experimental Section

Elemental analyses on either a Perkin-Elmer 240B or an F and M 185 analyzer were performed by Deanna Cardin or James Gould at the University of New Hampshire. IR spectra were recorded on a Perkin-Elmer 283 D grating instrument; solids were KBr pellets, and liquids were neat samples. ^1H NMR spectra were recorded on a JEOL FX 90Q at 90 MHz or on a Varian EM360A at 60 MHz. ^{13}C NMR spectra were recorded at 22.5 MHz on a JEOL FX 90Q instrument. UV–vis spectra were taken on a Varian/Cary 219 spectrophotometer interfaced with an Apple IIe computer. MS were obtained by William Dotchin, University of New Hampshire Instrumentation Center, on a Hitachi Perkin-Elmer RMU-6E instrument. TLC was performed on Baker-Flex Silica Gel IB-F on Mylar plates dried in an oven prior to use, with ether as eluent. Flash chromatography was peformed on a 38 mm diameter column packed with 6 in. of EM Reagent Kieselgel 60, 230–400 mesh ASTM, or Baker TLC Reagent, silica gel 7. HPLC was carried out with a Waters Associates Prep LC/System 500 through a PrepPak-500/silica column.

2-(2-Hydroxyethoxy)benzoic Acid, Methyl Ester (2a). Crude material prepared by Mobay Chemical Corp. from methyl salicylate and ethylene oxide was purified in three different ways. Vacuum distillation of 125-mL batches afforded reasonably pure material in 40% recovery, bp 100–110 °C (0.1 torr), 300 mL being collected in 2 h. The material was contaminated with lactone **1a**.

Flash chromatography of a 3-g sample (diethyl ether eluent, flow rate 2in./min) afforded two fractions: dilactone (0.2 g, R_f 0.87) and methyl ester **2a** (0.95 g, R_f 0.46).

For HPLC separation a solution of 20 g of vacuum-distilled material in 15 mL of ethyl acetate/15 mL of hexane was injected onto the column. Samples were collected in 250-mL portions with 40% ethyl acetate/60% hexane as eluent. Combining of fractions with identical R_f's, drying ($MgSO_4$), and concentration of the solutions afforded three compounds: dilactone (fractions 2 and 3, R_f 0.75, 2.0 g [10%]); monolactone **1a** (fractions 4 and 5, R_f 0.66, 2.0 g [10%]); methyl ester **2a** (fractions 6–11, R_f 0.48, 12.0 g [60%]).

Methyl ester 2a:[18] IR (film) 3600–3120, 3100, 3000–2850, 1720, 1610, 1590, 1300–1000, 760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.9–6.9 (m, 4 H, Ar H), 4.3–3.8 (m, 5 H, OCH_2CH_2OH), 3.8 (s, 3 H, OCH_3); ^{13}C NMR ($CDCl_3$) 166.73, 159.00, 133.83, 131.62, 121.02, 120.50, 115.23, 71.79, 60.93, 52.08 ppm; MS, *m/z* (relative intensity) 196 (32), 166 (41), 120 (100), 92 (67), 44 (7); UV (MeOH) 204.5 nm (ε 24 000), 229 (5160), 287.5 (2400).

Anal. Calcd for $C_{10}H_{12}O_4$ (196): C, 61.22; H, 6.16. Found: C, 61.13; H, 6.20.

Dilactone dibenzo[*f,m*]-2,5,9,12-tetraoxacyclotetradecane-1,8-dione: mp 164–165 °C; IR 3100, 1730, 1710, 1610, 1590, 750 cm^{-1}; ^1H NMR (acetone-d_6) δ 7.6–6.9 (m, 8, Ar H), 4.7–4.2 (m, 8, OCH_2CH_2O); ^{13}C NMR ($CDCl_3$) 168.10, 157.18, 133.11, 131.29, 121.43, 120.69, 112.24, 65.58, 63.27 ppm; MS, *m/z* (relative intensity) 328 (24), 191 (63), 164 (60), 120 (100), 92 (58).

Anal. Calcd for $C_{18}H_{16}O_6$ (328): C, 65.85; H, 4.91. Found: C, 65.66; H, 5.19.

Monolactone 1a:[18] bp 110–125 °C (0.1 mm) (Kugelrohr); mp 35–36 °C; IR (film) 3090, 3000–2800, 1720, 1610, 1590, 1300–1000, 760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.9–6.9 (m, 4, Ar H), 4.5 (s, 4, OCH_2CH_2O); ^{13}C NMR ($CDCl_3$) 169.00, 154.78, 134.87, 133.37, 122.58, 121.02, 119.39, 70.88, 65.46 ppm; MS *m/z* (relative intensity) 164 (77), 120 (22), 105 (100), 78 (10), 76 (36); UV (MeOH) 204.5 nm (ε 28 500), 233 (6700), 293 (2900).

Anal. Calcd for $C_9H_8O_3$ (164): C, 65.85; H, 4.91. Found: C, 65.66; H, 4.90.

2-(2-Hydroxyethoxy)benzamide (3a). A mixture of 6.0 g (0.03 mol) of distilled methyl ester **2a** and 100 mL of 30% NH_4OH was stirred at room temperature 1 h until homogeneous. The residue after concentration crystallized. It was recrystallized three times from ether/ethyl acetate (1:1, v/v): 3.0–4.1 g (55–75%); mp 112–113 °C (lit.[19] mp 114–116 °C); IR 3420–3200, 3100, 2950, 1665, 1595, 1570, 1450, 750 cm^{-1}; ^1H NMR (acetone-d_6) 8.2–6.9 (m, 6, Ar H, NH_2), 4.5–3.8 (m, 5, CH_2CH_2OH); ^{13}C NMR (acetone-d_6) 167.90, 158.34, 133.95, 132.46, 122.64, 121.73, 114.25, 71.66, 60.60 ppm; MS, *m/z* (relative intensity) 181 (10), 120 (100), 65 (10).

Anal. Calcd for $C_9H_{11}NO_3$ (181): C, 59.66; H, 6.12; N, 7.73. Found: C, 59.35; H, 6.22; N, 7.45.

2-(2-Hydroxethoxy)benzoic Acid (2c). A mixture of 4.5 g (0.025 mol) of amide **3a** and 50 mL of 20% HCl was heated at reflux 24 h, cooled, and extracted with 3 × 30 mL of methylene chloride. Extraction of the combined organic extracts with 3 × 30 mL of saturated $NaHCO_3$, acidification of the extracts, extraction with 3 × 30 mL of $CHCl_3$, and evaporation of the solvent afforded the acid: 3.0 g (67%); IR 3600–2500, 3100, 3000–2890,

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1730, 1610, 1590, 1300–1000, 760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.2–6.9 (m, 6, Ar H, COOH, OH), 4.4–3.9 (m, 4, OCH_2CH_2O); ^{13}C NMR ($CDCl_3$) 167.38, 158.15, 134.87, 132.98, 121.86, 118.46, 113.99, 71.33, 60.28 ppm; MS, m/z (relative intensity) 182 (4), 120 (100), 105 (73), 92 (83), 77 (36).

Anal. Calcd for $C_9H_{10}O_4$ (182): C, 59.34; H, 5.53. Found: C, 59.36; H, 5.48.

Preparation of Dinitro Lactone 1b. To a sample of 6.0 g (0.030 mol) of distilled **2a** chilled to 5 °C was added, with magnetic stirring, 15 mL of cold concentrated H_2SO_4 over a 5-min period, during which time the temperature rose to 28 °C. Once the dark brown, viscous oil had been cooled to 5 °C, a cold mixture of concentrated HNO_3 and H_2SO_4 (10 mL/10 mL) was added dropwise in 1.5 h, the temperature being maintained between 0–10 °C. The orange-brown mixture was poured slowly into 600 g of crushed ice with continuous, vigorous mechanical stirring. After the mixture had been refrigerated for 20 h, the solid was collected by filtration and washed with 50 mL of distilled water and air-dried to afford 6.0 g of crude off-white dinitro lactone. Recrystallization twice from acetone/diethyl ether gave the colorless product in 51% yield: mp 169–170 °C; IR 3100, 2950, 1690, 1630, 1600, 1550, 1350, 1300 cm^{-1}; ^1H NMR δ (Me_2SO-d_6) 9.1–8.9 (dd, 2 H, Ar), 5.0–4.7 (m, 4 H, OCH_2CH_2O); ^{13}C NMR (Me_2SO-d_6) 165.11, 151.71, 142.48, 140.01, 132.20, 124.01, 121.80, 73.55, 65.61 ppm; MS, m/z (relative intensity) 254 (100), 209 (40), 194 (74), 164 (8), 118 (34), 74 (35); UV (MeOH) 215 nm (ϵ 17 750), 272.5 (9600).

Anal. Calcd for $C_9H_6N_2O_7$ (254): C, 42.53; H, 2.38; N, 11.02. Found: C, 42.83; H, 2.14; N, 10.67.

3,5-Dinitro-2-(2-hydroxyethoxy)benzoic Acid, Methyl Ester (2b). A mixture of 3.0 g (0.012 mol) of dinitro lactone **1b**, 50 mL of absolute MeOH, and 3 drops of concentrated HCl was heated at reflux for 14 h. The cooled solution was neutralized with saturated $NaHCO_3$ and concentrated to 5 mL; after the addition of 25 mL of water the mixture was stirred and again neutralized with $NaHCO_3$. It was extracted with 3 × 20 mL of CH_2Cl_2; the combined organic extracts were washed with 50 mL of water, dried ($MgSO_4$), and concentrated in vacuo to give 3.2 g (95%) of the ester **2b** as a viscous, yellow oil: IR 3600, 3090, 2990, 1730, 1620, 1600, 1550, 1350, 1300 cm^{-1}; ^1H NMR δ ($CDCl_3$) 9.0–8.3 (dd, 2, Ar H), 4.4–3.8 (m, 4, OCH_2CH_2O), 3.6 (s, 3, OCH_3), 3.3 (s, 1, OH); ^{13}C NMR (Me_2SO-d_6) 163.25, 155.90, 144.46, 141.40, 129.50, 126.90, 123.52, 60.04, 54.84, 53.35 ppm; MS, m/z (relative intensity) 254 (26), 226 (62), 210 (80), 194 (100), 152 (35), 118 (30), 74 (30); UV (MeOH) 213.5 (ϵ 21 250), 272.5 (12 000).

Anal. Calcd for $C_{10}H_{10}N_2O_8$ (282): C, 41.97; H, 3.52; N, 9.79. Found: C, 41.72; H, 3.38; N, 9.67.

3,5-Dinitro-2-(2-hydroxyethoxy)benzamide (3b). Nitration of 3.0 g (0.0165 mol) of **3a** with a mixture of 15 mL of concentrated HNO_3/15 mL of concentrated H_2SO_4 at 0–5 °C for 3 h and workup as described for dinitro lactone **1b** afforded, after recrystallization from EtOH, 4.3 g (95%) of 3,5-dinitro-2-(2-hydroxyethoxy)-benzamide: mp 146–147 °C; IR 3500, 3100, 3000, 1680, 1640, 1590, 1350, 1300 cm^{-1}; ^1H NMR (acetone-d_6) δ 8.6–7.2 (m, 4, Ar H, NH_2), 5.0–4.5 (m, 4, OCH_2CH_2O), 3.8–3.4 (br s, 1, OH); ^{13}C NMR (acetone-d_6) 164.65, 161.73, 142.74, 128.69, 128.30, 124.27, 114.58, 71.92, 67.30 ppm; MS, m/z (relative intensity) 254 (100), 210 (5), 194 (57), 106 (34), 74 (19).

Anal. Calcd for $C_9H_9N_3O_7$ (271): C, 39.86; H, 3.35; H, 15.49. Found: C, 39.68; H, 3.18; N, 15.09.

3,5-Dinitrosalicylic Acid (4a). From Dinitro Lactone 1b. A mixture of 0.50 g (0.001 96 mol) of **1b** and a solution of 0.16 g (0.0040 mol) of sodium hydroxide in 15 mL of water was heated at reflux for 0.5 h. Acidification with CO_2 or concentrated HCl afforded 0.50 g (90%) of 3,5-dinitrosalicylic acid, sodium salt, which was recrystallized from water: mp 320 °C; IR 3600, 3420, 3100, 1610, 1380, 1530, 1340 cm^{-1}; ^1H NMR (Me_2SO-d_6) 8.7 (s, 2, Ar H), 3.9–3.5 (br s, 3, Ar OH, H_2O).

A samle of 0.80 g (0.0029 mol) of sodium salt from several experiments was acidified with 3 mL of concentrated H_2SO_4 and 5 mL of water. The white solid was recrystallized from water to afford 0.600 g (90%) of 3,5-dinitrosalicylic acid: mp 172–173 °C (lit.[20] mp 172–174 °C); mmp 172–173 °C; IR identical with that of the material prepared from 2-chloro-3,5-dinitrobenzoic acid and with Sadtler spectrum 17383; ^{1} H NMR spectrum identical with Sadtler spectrum 12836.

From 2b. A 0.50-g (0.00177 mol) sample of **2b** was heated in a solution of 0.15 g (0.0038 mol) of NaOH in 15 mL of water at 80 °C for 0.5 h. Direct acidification with concd H_2SO_4 gave a precipitate, which was recrystallized once from water to afford 0.30 g (77%) of 3,5-dinitrosalicylic acid, identical with that from **1b** (mp, IR).

From 2-Chloro-3,5-dinitrobenzoic Acid. From 1.0 g of 2-chloro-3,5-dinitrobenzoic acid heated with NaOH at 60 °C and workup as above there was obtained 0.8 g (86%) of 3,5-dinitrosalicylic acid, identical in every respect with samples prepared from **1b** or **2b**.

2-(Phenylthio)-3,5-dinitrobenzoic Acid (4b). From Dinitro Lactone 1b. A mixture of 0.50 g (0.00196 mol) of **1b**, 10 mL of absolute methanol, and 3.3 mL (0.006 mol) of potassium thiophenoxide solution (prepared from benzenethiol and 1.0 equiv of KOH in absolute MeOH) was stirred 0.5 h at room temperature and then at 50 °C for 15 min. The clear yellow solution was cooled and acidified with 10% HCl. The yellow solid was collected by suction and recrystallized from MeOH to afford 0.59 g (96%) of 2-(phenylthio)-3,5-dinitrobenzoic acid: mp 200–201 °C (aqueous EtOH); mmp 200–202 °C; ^1H NMR identical with that of material prepared from 2-chloro-3,5-dinitrobenzoic acid.

From 2b. Treatment of 0.50 g (0.001 74 mol) of **2b** with 0.57 g (0.0039 mol) K thiophenoxide and workup as above afforded 0.45 g (92%) of 2-(phenylthio)-3,5-dinitrobenzoic acid: mp 199–200 °C; mmp 198–201 °C; IR identical with that of material prepared from 2-chloro-3,5-dinitroenzoic acid.

From 2-Chloro-3,5-dinitrobenzoic Acid. After treatment of 0.50 g (0.002 mol) of 2-chloro-3,5-dinitrobenzoic acid in 10 mL of absolute methanol with 0.65 g (0.0044 mol) of methanolic K thiophenoxide for 1 h at room temperature the reaction mixture was acidified with 10 mL of water and 1 mL of HCl. The slurry was stirred in an ice bath for 1 h; the yellow solid was collected by suction and recrystallized once from ethanol/water to yield 0.63 g (97%) of 2-(phenylthio)-3,5-dinitrobenzoic acid:[21] mp 200–202 °C; IR 3500–2500, 3100, 1700, 1610, 1590, 1540, 1350, 1300; ^1H NMR (acetone-d_6) δ 9.7–9.4 (br s, 1, COOH), 8.9–8.5 (dd, 2, Ar H), 7.3 (s, 5, Ar H); ^{13}C NMR (acetone-d_6) 165.04, 153.27, 146.84, 140.14, 139.03, 133.89, 132.72, 130.25, 129.47, 128.11, 122.58 ppm; MS, m/z (relative intensity) 320 (100), 210 (36), 182 (43), 166 (45), 125 (58), 77 (53).

Anal. Calcd for $C_{13}H_8N_2O_6S$ (320): C, 48.75; H, 2.51; N, 8.74. Found: C, 48.96; H, 2.57; N, 8.56.

2-Amino-3,5-dinitrobenzamide (4c). From Dinitro Lactone 1b. A mixture of 0.5 g (0.002 mol) of **1b** and 50 mL of 30% NH_4OH was heated on a steam bath with stirring until the white solid had completely disappeared and a yellow solid had formed. The mixture was heated an additional hour and then cooled in an ice bath. The solid was collected and recrystallized once from water to afford 0.40 g (90%) of amide: mp 280–283 °C (lit.[22] mp 284 °C); IR 3500–3200, 3100, 1690, 1640, 1570, 1350 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 9.5–9.0 (br s, 2, NH_2), 9.0–8.8 (dd, 2, Ar H), 8.7–8.4 (br s, 1, NH), 8.2–7.8 (br s, 1, NH); ^{13}C NMR (Me_2SO-d_6) 168.45, 149.27, 133.33, 131.06, 129.95, 125.66, 118.31 ppm; MS, m/z (relative intensity) 226 (100), 209 (20), 117 (19), 90 (19), 62 (21).

Anal. Calcd for $C_7H_6N_4O_5$ (226): C, 37.18; H, 2.67; N, 24.77. Found: C, 37.46; H, 2.61; N, 24.42.

From Ester 2b. From 0.5 g (0.00174 mol) of **2b** and 10 mL of 30% NH_OH at room temperature there was obtained 0.39 g (100%) of amide, mp, after one recrystallization from water, 282–284 °C, identical in all respects with that obtained from **1b**.

2-(Methylamino)-3,5-dinitro-*N*-methylbenzamide (4d). From Dinitro Lactone 1b. A mixture of 25 mL (0.32 mol) of 40% aqueous methylamine and 1.0 g (0.00394 mol) of **1b** was stirred at room temperature for 8 h. The yellow solid (0.4 g) was collected, and the filtrate, concentrated at room temperature for 2 days, afforded an additional 0.6 g of solid. Recrystallization from water provided a total of 1.0 g (100%) of amide: mp 174–175

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°C; IR (KBr) 3360–3300, 3100, 3000, 1645, 1620, 1590, 1550, 1320 cm^{-1}; ^1H NMR (acetone-d_6) δ 9.6–9.0 (br s, 0.5, NH), 8.9–8.3 (dd, 2, Ar H), 8.3–7.8 (br s, 0.5, NH), 3.2–2.8 (m, 7, 2 NCH_3 and NH); ^{13}C NMR (acetone-d_6) 167.84, 149.18, 134.80, 134.15, 129.60, 125.37, 124.53, 32.58, 26.85, 26.72 ppm; MS, m/z (relative intensity) 254 (44), 237 (100), 206 (59), 150 (42), 131 (46), 76 (70).

Anal. Calcd for $C_9H_{10}N_4O_5$ (254): C, 42.53; H, 3.97; N, 22.04. Found: C, 42.43; H, 3.99; N, 22.29.

From Ester 2b. From 0.50 g (0.00174 mol) of ester **2b** and excess aqueous methylamine was obtained 0.44 g (99%) of amide. It was recrystallized once from ethanol/water: mp 173–175 °C; mmp 173–175 °C; IR and ^1H NMR (acetone-d_6) were identical with those of the material prepared from dinitro lactone.

2-(Dimethylamino)-3,5-dinitro-*N*,*N*-dimethylbenzamide (4e). From Dinitro Lactone 1b. A mixture of 25 mL (0.138 mol) of 25% aqueous dimethylamine and 1.0 g (0.00394) of **1b** was stirred at room temperature for 0.5 h and then heated until the solid had dissolved. The solution was allowed to evaporate at room temperature for 2 days, and the yellow-orange solid was collected and recrystallized once from water to give 1.0 g (94%) of amide:[23] mp 107–109 °C; IR 3080, 2950, 1650, 1610, 1590, 1540, 1335 cm^{-1}; ^1H NMR (acetone-d_6) δ 8.7–8.1 (dd, 2, Ar H), 3.2 (s, 3, NCH_3), 3.0–2.95 (2 s, 9, NCH_3 and $N(CH_3)_2$); ^{13}C NMR (acetone-d_6) 167.78, 147.94, 141.11, 138.51, 132.33, 128.04, 123.94, 42.59, 38.56, 34.92 ppm; MS, m/z (relative intensity) 282 (4), 190 (100), 146 (17), 102 (4).

Anal. Calcd for $C_{11}H_{14}N_4O_5$ (282): C, 46.81; H, 5.00; N, 19.85. Found: C, 46.87; H, 5.00; N, 19.68.

From Ester 2b. From 0.50 g of **2b** and excess dimethylamine at room temperature after 8 h there was obtained 0.40 g (82%) of amide: mp 105–106 °C (EtOH/water); mmp 106–107 °C; IR and ^1H NMR identical with those of material prepared from dinitro lactone.

2-(Phenylamino)-3,5-dinitrobenzoic Acid (4f) and the Anilinium Salt. From Dinitro Lactone 1b. A mixture of 0.5 g (0.002 mol) of **1b**, 25 mL of 95% ethanol, and 0.2 mL (0.002 mol) of aniline was heated at reflux for 24 h. When cooled to room temperature, it deposited 0.2 g of unchanged dinitro lactone: mp 171–172 °C; mmp 170–172 °C; IR was identical with that of the starting material. The filtrate was concentrated under reduced pressure to give an orange liquid, which was dissolved in 3 mL of diethyl ether and chloroform. When chilled in an ice bath, the solution deposited 0.30 g (76%) of 2-(phenylamino)-3,5-dinitrobenzoic acid, anilinium salt: mp 184–185 °C; IR identical with that of the material prepared from 2-chloro-3,5-dinitrobenzoic acid.

A 0.25-g (0.0063 mol) sample of anilinium salt in 5 mL of 10% aqueous HCl was heated to 90 °C and stirred for 0.5 h. The yellow mixture was cooled in an ice bath; solid was collected by suction and air-dried to afford 0.15 g (80%) of 2-(phenylamino)-3,5-dinitrobenzoic acid (**4f**): mp 213–214 °C; mmp 212–214 °C; IR, ^1H NMR (acetone-d_6), ^{13}C NMR (acetone-d_6), and MS were all identical with those of material prepared from 2-chloro-3,5-dinitrobenzoic acid.

From 2-Chloro-3,5-dinitrobenzoic Acid. A mixture of 2.0 g (0.0081 mol) of 2-chloro-3,5-dinitrobenzoic acid and 3 mL of freshly distilled aniline was stirred under N_2 at room temperature for 0.5 h, at which point 15 mL of diethyl ether was added. The orange solid was collected by suction, rinsed several times with ether, and recrystallized from ethanol to afford 2.3 g (72%) of 2-(phenylamino)-3,5-dinitrobenzoic acid, anilinium salt: mp 183–185 °C (lit.[20] mp 192 °C); IR 3300–2600, 3100, 1600, 1540, 1500, 1360 cm^{-1}; ^1H NMR δ (acetone-d_6) δ 9.2–8.8 (dd, 3, NO_2ArH and NH), 7.5–6.9 (m, 13, Ar H and NH_3^+); ^{13}C NMR (Me_2SO-d_6) 167.71, 144.33, 142.18, 139.59, 136.59, 135.81, 130.86, 129.56, 129.37, 126.18, 125.53, 121.43, 120.78, 120.00, 117.66 ppm.

Anal. Calcd for $C_{19}H_{16}N_4O_6$ (396): C, 57.58; H, 4.07; N, 14.14. Found: C, 57.46; H, 4.03, N, 14.16.

A 1-g (0.0025 mol) sample of the anilinium salt was heated with 50 mL of 10% HCl at 45 °C for 15 min. The mixture was cooled in an ice bath, and the yellow solid was collected by suction, recrystallized from ethanol, and air-dried to afford 0.75 g (98%) of 2-(phenylamino)-3,5-dinitrobenzoic acid: mp 213–214 °C (lit.[24] mp 214 °C); IR 3260, 3200–2500, 3100, 1690, 1600, 1550, 1350 cm^{-1}; ^1H NMR (acetone-d_6) δ 10.9 (br s, 1, COOH), 9.9 (br s, 1, NH), 9.1–8.8 (dd, 2, NO_2Ar H), 7.3–6.9 (m, 5, Ar H); ^{13}C NMR (acetone-d_6) 168.10, 145.40, 140.07, 138.19, 137.02, 131.94, 130.19, 127.91, 126.74, 121.28, 118.03 ppm; MS, m/z (relative intensity) 303 (100), 268 (19), 193 (16), 165 (40), 77 (26).

Anal. Calcd for $C_{13}H_9N_3O_6$ (303); C, 51.49; H, 2.99; N, 13.86. Found: C, 51.38; H, 2.93; N, 13.83.

2-Methoxy-3,5-dinitrobenzoic Acid (4g). From 2-Chloro-3,5-dinitrobenzoic Acid. From a mixture of 1.0 g (0.004 mol) of 2-chloro-3,5-dinitrobenzoic acid and 0.35 g of NaOH in 4 mL of absolute MeOH, stirred at room temperature for 70 min, there was collected by suction 1.0 g (93%) of the Na salt as a yellow powder: IR (KBr) 3100, 1640, 1400, 1560, 1350, 1300 cm^{-1}. Acidification of a 0.30-g. sample of the salt in 10 mL of water with concentrated HCl afforded 0.25 g (91%) of the acid: mp 164–165 °C, after two recrystallizations from $MeOH/H_2O$ (lit.[20] mp 165 °C); IR (KBr) 3200–2500, 3100, 2950, 1700, 1620, 1590, 1560, 1350, 1300 cm^{-1}; ^1H NMR (acetone-d_6) δ 10.7 (s, 1, COOH), 8.9 (s, 2, Ar H), 4.15 (s, 3, OMe); ^{13}C NMR (acetone-d_6) 164.07, 158.22, 145.99, 142.93, 130.77, 128.82, 124.14, 65.16 ppm; MS, m/z (relative intensity) 242 (5), 194 (100), 120 (15), 92 (19), 74 (12).

Anal. Calcd for $C_8H_6N_2O_7$: C, 39.68; H, 2.50; N, 11.57. Found: C, 39.42; H, 2.44; N, 11.40.

From Dinitro Lactone 1b. A 1.0-g (0.004 mol) sample of **1b** and 15 mL of NaOMe solution (prepared from 0.20 g Na) was heated at reflux for 3 h, and then the mixture was cooled to room temperature. Solid was removed by suction, and the filtrate was diluted with 10 mL of water and then acidified with 3 N HCl. The white solid was collected and recrystallized twice from MeOH/water to give 0.70 g (72%) of the acid: mp 164–165 °C; mmp 164–165 °C; IR, ^1H NMR, ^{13}C NMR, and MS were identical with those of material prepared from 2-chloro-3,5-dinitrobenzoic acid.

From Ester 2b. When 0.5 g (0.0018 mol) of **2b** and 15 mL of NaOMe (from 0.2 g Na) were combined at room temperature, an orange solid (subsequently shown to be Meisenheimer complex A) precipitated. The mixture was heated at reflux for 3 h; the small amount of sodium 2-methoxy-3,5-dinitrobenzoate (5%) was removed by filtration, and the filtrate was concentrated to dryness, the residue taken up in 10 mL of water, and the solution acidified with 10% HCl. The precipitated acid (85%), recrystallized from water, was identical in all respects with that from 2-chloro-3,5-dinitrobenzoic acid.

Preparation of the Potassium Salt 7a and Phenolic Thiocyanatoethyl Ester 7b by Cleavage of Dinitro Lactone 1b with Potassium Thiocyanate. A mixture of 0.75 g (0.00295 mol) of **1b**, 1.5 g (0.015 mol) of potassium thiocyanate, and 5.5 mL of dry Me_2SO was heated under N_2 at 110 °C for 3 h. TLC (diethyl ether as the eluent) indicated disappearance of starting material after 1.5 h. The orange solution was poured slowly with vigorous stirring into 25 g of crushed ice, and the mixture was refrigerated for 12. The lustrous, yellow solid was collected by suction to afford 1.0 g (97%) of salt **7a**. After one recrystallization from ethanol/water, it was obtained as a fine yellow powder: mp 270 °C, darkened; decomposes violently at 340 °C; IR (KBr) 3600–3400 (H_2O), 3100, 2170, 1725, 1600, 1560, 1340, 1300–1000 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 8.6–8.4 (dd, 2, Ar H), 4.6–4.3 (m, 2, OCH_2), 3.6–3.3 (m, 2, OCH_2); ^{13}C NMR (Me_2SO-d_6) 167.06, 164.59, 140.33, 131.16, 125.44, 122.71, 112.73, 61.84, 32.45 ppm; UV (MeOH) 243 nm (ε 16 100), 265 (16 400), 365 (16 500).

Anal. Calcd for $C_{10}H_6N_3O_7S{\cdot}0.5\ H_2O$ (360): C, 33.33; H, 1.94; N, 11.65. Found: C, 32.98; H, 1.65; N, 11.26.

A solution of 0.25 g (0.00071 mol) of **7a** in 25 mL of hot water was acidified to pH 2 with 2 drops concentrated HCl. The mixture was chilled in an ice bath and the solid (0.22 g) collected by suction. One recrystallization from acetone/water afforded 0.20 g (91%) of a yellow-white, crystalline compound identified as 3,5-dinitrosalicylic acid, 2-thiocyanatoethyl ester (**7b**): mp 139–140 °C; IR (KBr) 3100, 2900, 2160, 1690, 1625, 1600, 1545, 1360, 1300–1000 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 8.9–8.8 (m, 2, Ar H), 4.9 (s, 1, OH), 4.8–4.6 (m, 2, OCH_2) 3.6–3.4 (m, 2, CH_2O); ^{13}C NMR (Me_2SO-d_6) 164.81, 157.59, 138.73, 137.11, 129.89, 125.47, 118.70, 113.11, 64.47,

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32.28 ppm; MS, m/z (relative intensity) 313 (5), 255 (3), 108 (50), 86 (100); UV (MeOH) 209.5 nm (ϵ 19000), 281 (4600), 358.5 (11200).

Anal. Calcd for $C_{10}H_7N_3O_7S$ (313): C, 38.34; H, 2.24; N, 13.41. Found: C, 38.36; H, 2.21; N, 13.49.

Hydrolysis of 7a and 7b to 3,5-Dinitrosalicylic Acid. Base Hydrolysis of 7a. A solution of 0.20 g (0.00071 mol) of the K salt **7a**, 0.1 g of KOH, and 10 mL of water was heated at 80 °C for 15 min and then cooled to room temperature. The clear yellow solution was extracted with 30 mL of diethyl ether; the aqueous layer was acidified with concentrated sulfuric acid. The precipitated white solid was collected by suction and air-dried to yield 0.15 g (94%) of 3,5-dinitrosalicylic acid: mp 170–171 °C (lit.[25,26] mp 170 °C; 173 °C); mmp 169–170 °C; IR (KBr) identical with that of material prepared from 2-chloro-3,5-dinitrobenzoic acid.

Acid Hydrolysis of 7a. A mixture of 0.25 g (0.00071 mol) of **7a**, 1 mL of concentrated HCl, and 12 mL of water was heated at reflux for 4 h. The remaining solid (0.05 g), collected by suction from the hot mixture and air-dried, was identified as the phenolic thiocyanatoethyl ester **7b**: mp 139–140 °C; mmp 139–140 °C. A second solid (0.10 g, 63%), collected and air-dried from the chilled filtrate, was identified as 3,5-dinitrosalicylic acid: mp 169–170 °C; mmp 169–172 °C; IR identical with that obtained from **7a** above.

Acid Hydrolysis of 7b. A solution of 0.50 g (0.0016 mol) of ester **7b** in 10 mL of 20% aqueous sulfuric acid was heated at reflux for 3 h. It was cooled in an ice bath, and the solid was collected by suction to afford 0.32 g (88%) of 3,5-dinitrosalicylic acid: mp 171–173 °C; mmp 171–172 °C; IR identical with that obtained above from **7a**.

Meisenheimer Complex A. From Dinitro Methyl Ester 2b. To a solution of NaOMe, prepared from 0.10 g of Na metal and 15 mL of absolute MeOH, was added with stirring under nitrogen a solution of 0.50 g (0.00017 mol) of **2b** in 5 mL of absolute MeOH. After 30 min at room temperature the orange solid was collected, rinsed with absolute MeOH, and recrystallized from EtOH or MeOH/water to afford 0.55 g (94%) of the Meisenheimer Complex A: mp 192–193 °C (discolors at 175 °C); IR (KBr) 3650–3200, 3110, 1690, 1530, 1330 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 8.5–8.0 (dd, 2, alkene), 4.2 (s, 4, (OCH_2CH_2O), 3.7 (s, 3, OCH_3), 3.4 (s, 1, OH), 3.2 (s, 3, OCH_3); ^{13}C NMR (Me_2SO-d_6) δ 165.50, 128.95, 127.98, 125.57, 119.07, 116.21, 107.04, 69.19, 50.91, 48.44; MS, m/z (relative intensity) 254 (6), 194 (5), 44 (100); UV (acetone) 388 nm (ϵ 22300), 474.5 (22350).

Anal. Calcd for $C_{11}H_{13}N_2O_9Na$ (340): C, 38.83; H, 3.84; N, 8.23. Found: C, 38.62; H, 3.54; N, 8.50.

From Dinitro Lactone 1b. In a similar manner from 0.5 g of dinitro lactone **1b** there was obtained 0.60 g (91%) of the Complex A: mp, IR, and UV identical with those of material as prepared from **2b**.

Spiro Meisenheimer Complex B. From 2b with Thiophenoxide. A solution of 0.50 g (0.00177 mol) of dinitro ester, 0.29 g (0.00194 mol) of K thiophenoxide, and 5 mL of absolute MeOH was stirred at room temperature for 4 h, during which time a yellow solid precipitated. This was collected, rinsed with 3 × 10 mL of MeOH, and dried to give 0.550 g (97%) of spirocyclic complex B: mp 230 °C dec. (discolors at 220 °C) (one recrystallization from MeOH/water); IR (KBr) 3100, 3000, 1690, 1520, 1330 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 8.5–8.0 (m, 2, alkene), 4.1 (s, 4, OCH_2CH_2O), 3.8 (s, 3, OCH_3); ^{13}C NMR (Me_2SO-d_6) 165.59; 129.04, 128.07, 125.66, 119.16, 116.30, 107.06, 69.28, 51.01 ppm; MS, m/z (relative intensity) 254 (100), 194 (69), 118 (34), 74 (38), 62 (70), 53 (31); UV (acetone) 388 nm (ϵ 23760), 475 (23780).

Anal. Calcd for $C_{10}H_9N_2O_8K$ (324): C, 37.03; H, 2.79; N, 8.63. Found: C, 37.42; H, 2.67; N, 8.81.

From 1b with Thiophenoxide. A suspension of 0.50 g (0.00196 mol) of dinitro lactone and 5 mL of absolute methanol was stirred for 5 min at room temperature and then treated with 0.28 g (0.00194 mol) of potassium thiophenoxide in 1 mL of absolute methanol. Stirring was maintained for 2 h at room temperature, and then the remaining solid was collected by suction and rinsed with methanol to afford 0.10 g of recovered dinitro lactone: mp 169–170 °C; mmp 169–170 °C; IR (KBr) identical with that of the starting material. The clear, yellow filtrate was stirred at room temperature for 2 h, during which time a yellow solid precipitated. It was collected by suction and rinsed with MeOH to yield 0.455 g (90%) (calcd from 0.40 g of dinitro lactone) of spirocyclic Meisenheimer complex: IR and ^1H NMR (acetone-d_6 and Me_2SO-d_6) identical with those of material prepared as from **2b**.

From 2b with KCN. The red solution resulting from combining 0.50 g (0.00196 mol) of **2b**, 0.12 g (0.00184 mol) of KCN, and 15 mL of absolute MeOH was stirred at room temperature for 35 min; the resulting orange solid was collected by suction and washed with absolute MeOH to afford 0.35 g (63%) of spirocyclic Meisenheimer complex B: IR and ^1H NMR (Me_2SO-d_6) identical with those of material prepared above.

From 1b with KCN. Similar treatment of 0.5 g of dinitro lactone **1b** afford 0.60 g (95%) of identical Meisenheimer complex B.

Interconversion of Meishenheimer Complexes. I. B to A with Methoxide. The orange-red mixture from NaOMe (from 0.20 g of Na metal and 6 mL of absolute MeOH) and 0.20 g of B was stirred under nitrogen at room temperature for 1 h. A 3-mL aliquot of the suspension afforded, after suction, 0.10 g of the Meisenheimer complex A, identical by IR to material prepared earlier.

II. A to B with Thiophenoxide. A mixture consisting of a suspension of 0.15 g of Meisenheimer complex A, 0.086 g of KSPh, and 2.3 mL of absolute MeOH was stirred at room temperature for 0.5 h, during which time the orange solid dissolved and a new yellow solid precipitated. This was collected by suction, rinsed several times with absolute MeOH, and recrystallized once from MeOH to afford 0.12 g (84%) of spirocyclic Meisenheimer complex B: IR (KBr) and ^1H NMR (Me_2SO-d_6) were identical with those of material prepared from **1b**.

III. A to B in Acetone. A solution of 0.1 g of A in 3 mL of dry acetone was stirred at room temperature for 30 min. The solvent was removed in vacuo and the residual solid recrystallized once from EtOH to give 0.08 g (84%) of B, identical by IR and ^1H NMR with material prepared elsewhere.

Conversion of A or B to 2-(2-Hydroxyethoxy)-3,5-dinitrobenzoic Acid, Methyl Ester (2b). A mixture of 0.15–0.20 g of A or B in 10 mL of 20% HCl was stirred at room temperature for 1 h and then heated briefly to 40–50 °C until the solid dissolved. The solution was immediately chilled in an ice bath and extracted with 3 × 15 mL of methylene chloride. The combined organic extracts were washed with $NaHCO_3$ and water, dried, and concentrated to afford in 90% yield the methyl ester **2b**, identical by IR and ^1H NMR with material prepared directly from **1b** and MeOH/HCl.

3,5-Dinitrosalicylic Acid (4a). From Meisenheimer Complex A. The dark red mixture from 0.20 g of Meisenheimer complex A and 5 mL of an aqueous solution containing 0.20 g of NaOH was stirred for 1.5 h at room temperature. Then it was heated to 60 °C and held at that temperature for 10 min after complete dissolution of the solid. The solution was chilled in an ice bath and treated with concentrated HCl. The precipitated yellow solid (0.14 g) was sodium 3,5-dinitrosalicylate, as shown by IR comparison with an authentic sample. Acidification of a 0.13-g sample with 4 mL of 25% H_2SO_4 afforded, after one recrystallization from water, 0.11 g (95%) of acid **4a**: mp 171–172 °C; mmp 171–172 °C; IR was identical with that of material prepared from 2-chloro-3,5-dinitrobenzoic acid.

From Meisenheimer Complex B. In a similar manner 0.15 g of B and aqueous NaOH was heated at reflux for 5 min and then at room temperature for 1 h. Acidification with HCl and recrystallization of the solid from water afforded acid **4a** in 93% yield.

2-Methoxy-3,5-dinitrobenzoic Acid (4g). From Meisenheimer Complex A. A mixture of 0.25 g of A in a solution of 0.20 g of Na metal and 15 mL of absolute MeOH was heated at reflux for 1 h. The red solution was cooled and the resulting mixture filtered. Removal of MeOH from the filtrate gave a maroon solid, which, on treatment with 15 mL of 10% HCl, afforded a nearly white solid. After one recrystallization from water there was obtained 0.15 g (88%) of the acid **4g**: mp 164–165 °C; mmp 164–165 °C; IR and ^1H NMR were identical with those

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of material prepared from 2-chloro-3,5-dinitrobenzoic acid.

From Meisenheimer Complex B. The orange suspension obtained (see above) from NaOMe and Meisenheimer Complex B in MeOH after 1 h of stirring at room temperature was heated at reflux for 3 h. The yellow solid was collected by suction to afford 2-methoxy-3,5-dinitrobenzoic acid, Na salt: IR was identical with that of the material prepared from 2-chloro-3,5-dinitrobenzoic acid. Treatment of 0.125 g of the salt with 20% HCl at 50 °C afforded 0.10 g of the acid **4g**: mp 164–165 °C; mmp 164–165 °C; IR was identical with that of the material prepared from 2-chloro-3,5-dinitrobenzoic acid.

2-(Phenylthio)-3,5-dinitrobenzoic Acid (4b). From Meisenheimer Complex A. The orange-red suspension obtained by combining 0.20 g (0.000 58 mol) of A and 0.288 g (0.001 95 mol) of potassium thiophenoxide, each dissolved in 1 mL of absolute MeOH, was stirred at room temperature for 0.5 h and then at 50 °C for 0.5 h until all solid had dissolved. The clear orange solution was cooled in an ice bath and acidified with 5% aqueous HCl until a solid precipitated from the solution. This was collected by suction and recrystallized once from ethanol/water to afford 0.15 g (85%) of the acid **4b**: mp 200–202 °C; mmp 200–202 °C; IR and ^{1}H NMR (acetone-d_6) were identical with those of material prepared from 2-chloro-3,5-dinitrobenzoic acid.

From Meisenheimer Complex B. A mixture of 0.15 g (0.000 46 mol) of B in 4 mL of absolute MeOH and a solution of 0.288 g (0.001 95 mol) of potassium thiophenoxide in 1 mL of absolute MeOH were combined and stirred at room temperature for 1 h and then at 50 °C for 15 min. After acidification and workup as above, the acid **4b** (95% crude yield) was identical with other samples (mmp, ^{1}H NMR).

2-Amino-3,5-dinitrobenzamide (4c) from Meisenheimer Complex A. A mixture of 0.20 g (0.000 58 mol) of Meisenheimer complex A and 5 mL of 30% aqueous NH_4OH was stirred for 1 h at room temperature, then at 60 °C until all the solid had dissolved, and then an additional 5 min, until a solid began to precipitate. The mixture was cooled in an ice bath and a bright yellow solid was collected by suction. After one recrystallization from water, 0.10 g (85%) of the amide **4c** was obtained: mp 280–282 °C; mmp 279–281 °C; IR and ^{1}H NMR (Me_2SO-d_6) were identical with those of material prepared from **1b**.

From Meisenheimer Complex B. A suspension of 0.15-g (0.000 47 mol) of Meisenheimer complex B and 5 mL of 30% aqueous NH_4OH was stirred at 50 °C until all solid had dissolved. After the solution had been cooled in an ice bath there was obtained 0.10 g (94%) of **4c**: mp (after one recrystallization from water) 280–282 °C; mmp 278–281 °C; IR and ^{1}H NMR were identical with those of material prepared from **1b**.

2-(Dimethylamino)-3,5-dinitro-*N*,*N*-dimethylbenzamide (4e) from Meisenheimer Complex B. A mixture of 7 mL of aqueous 25% dimethylamine and 0.15 g (0.000 47 mol) of Meisenheimer Complex B was stirred at room temperature for 12 h and then heated on a steam bath to concentrate the volume to 2 mL. The solid was collected by suction to afford 0.12 g (90%) of the amide **4e**, which was recrystallized from ethanol/water: mp 105–106 °C; mmp 106–107 °C; IR and ^{1}H NMR (acetone-d_6) were identical with those of material prepared from **1b**.

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Preparation of Potential Intermediates for the Synthesis of Yohimbine and Reserpine

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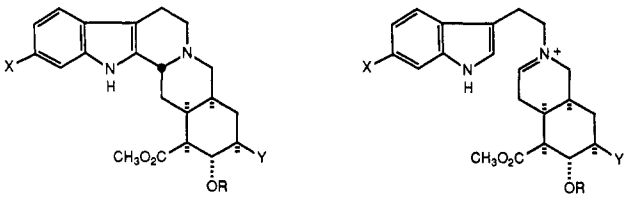
Norborn-5-ene-2-carboxaldehyde is converted by common synthetic intermediates into potential synthons for the ring D–E segment of 3-epi-α-yohimbine and reserpine.

The yohimbine alkaloids and reserpine represent molecules of challenging complexity and significant pharmacological importance.[3] Renewed synthetic interest in this area, as evidenced by several recent reports,[4] prompts us to disclose our own progress in this area.

We envisioned the stereospecific construction of reserpine[3a] (**1a**) and 3-epi-α-yohimbine[3b] (**1b**) from stereoelectronically allowed[5] capture of the tetrahydropyridinium ions **2a** and **2b** by the 2-position of the indole ring. This process would generate the 3-epialloyohimbane pentacyclic ring system. The tetrahydropyridinium salts **2** may be formed by condensation[6] of a suitably substituted trypt-



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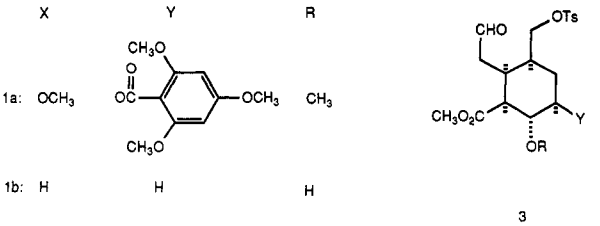

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