9.0 mmol) was added to the mixture. After the mixture was stirred for 4 h at room temperature, the reaction was quenched with water (20 mL), and the mixture was extracted with ether. The extract was washed with brine, dried over sodium sulfate, and concentrated in vacuo to give carbonyl compound **5**, which was purified by column chromatography, if necessary. The products were identified with authentic samples. The complex of dimethyl selenide and NCS was easily isolated (97%) in ether instead of toluene; however, it was very hygroscopic and gradually decomposed at room temperature.

1-Phenyl-2-(trimethylsilyl)propenone: bp 110 °C (3 torr, Kugelrohr); IR (neat) 1650 cm^{-1}; NMR ($CDCl_3$) δ 0.21 (s, 9 H), 6.01 (d, J = 2.4 Hz, 1 H), 6.10 (d, J = 2.4 Hz, 1 H), 7.20–7.60 (m, 3 H), 7.70–7.97 (m, 2 H).

Oxidation of β-Hydroxy Selenide 8. To a stirred solution suspension of NCS (1.00 g, 7.5 mmol) in dry toluene (30 mL) was added **8** (1.28 g, 5.0 mmol) in toluene (10 mL) under N_2 with cooling in an ice bath. After the mixture was stirred for 1 h at 0 °C, DBU (1.37 g, 9 mmol) was added to the mixture, and stirring was continued for 6 h at room temperature. Oily residue obtained by a workup as above was chromatographed on silica gel to give 1.02 g (81%) of 2-(phenylseleno)cyclohexanone (**9**): bp 115 °C (3 torr, bath temperature); IR (neat) 1700, 1570 cm^{-1}; NMR ($CDCl_3$) δ 1.42–2.53 (m, 7 H), 2.60–3.31 (m, 1 H), 3.80–4.07 (m, 1 H), 7.10–7.43 (m, 3 H), 7.43–7.73 (m, 2 H). The compound **9** was identified with an authentic sample prepared from lithium cyclohexanone enolate and phenylselenenyl bromide.

Oxidation of γ-Hydroxy Selenide 10. When this reaction was carried out under conditions similar to those for **8** for 7 h after addition of DBU, 2-benzylidenecyclohexanol (**11**) and diphenyl diselenide were obtained in 97% and 40% yields (preparative TLC), respectively. For the product **11**: IR (neat) 3600–3150, 1625, 1600, 1570 cm^{-1}; NMR ($CDCl_3$) δ 1.07–3.67 (m, 9 H), 4.07–4.37 (m, 0.7 H), 4.72–7.90 (m, 0.3 H), 6.33 (m, 0.3 H), 6.53 (br s, 0.7 H), 6.87–7.75 (m, 5 H); mass spectrum (70 eV), m/e 188 (M^+). The reaction for 14 h after addition of DBU gave a complicated mixture, which was chromatographed on silica gel and then purified by preparative GLC to afford **11** (75%), 2-benzylidenecyclohexanone (**12**, 15%), 3-benzylidenecyclohexene (**13**, 5%), and diphenyl diselenide (~50%). Enone **12**: IR (neat) 1680, 1600, 1570 cm^{-1}; NMR ($CDCl_3$) δ 1.45–2.32 (m, 4 H), 2.32–3.18 (m, 4 H), 7.12–7.62 (m, 6 H); mass spectrum (70 eV), m/e 186 (m^+). Diene **13**: IR (neat) 1600 cm^{-1}; NMR ($CDCl_3$) δ 1.45–2.98 (m, 6 H), 5.82–6.35 (m, 2 H), 7.25 (m, 6 H); mass spectrum (70 eV), m/e 170 (M^+).

Cross-reaction of **8** or **10** was carried out as follows. 4-*tert*-Butylcyclohexanol was added to a stirred solution of **8** or **10** (5.0 mmol) and NCS (0.60 g, 4.5 mmol) in dry toluene (30 mL) with cooling. After addition of DBU (0.76 g, 5.0 mmol) and stirring of the mixture for 5 h at room temperature, the reaction was quenched and worked up as usual. Yields of the products were determined by GLC and NMR.

2-(1-Hydroxybenzyl)cyclohexanol (16). Hydrogen peroxide (30%, 4.7 mL) in THF (5 mL) was added over 30 min to a stirred solution of γ-hydroxy selenide **10** (1.50 g, 4.3 mmol) in THF (20 mL) under N_2 with cooling in an ice bath, and stirring was continued for an additional 4.5 h at 0 °C. After addition of water (20 mL), the reaction mixture was extracted with ether, washed with sodium carbonate and brine, and dried over sodium sulfate. Evaporation of the solvent gave 0.63 g (71%) of **16**: mp 125–126 °C (ether); IR (Nujol) 3650–3100 cm^{-1}; NMR ($CDCl_3$) δ 0.73–2.20 (m, 9 H), 3.53 (m and s, 3 H, 2 OH and CH), 4.53 (d, J = 11.0 Hz, 1 H), 7.27 (m, 5 H); mass spectrum (70 eV), m/e 206 (M^+). Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.66; H, 8.81.

Registry No. **1** (R^1 = R^2 = Me), 593-79-3; **1** (R^1 = Me; R^2 = Ph), 4346-64-9; **1** (R^1 = R^2 = Ph), 1132-39-4; **2** (R^1 = R^2 = Me), 83845-67-4; **8**, 35446-84-5; **9**, 50984-16-2; **10** (isomer 1), 83845-68-5; **10** (isomer 2), 83915-67-7; (*E*)-**11**, 50648-70-9; (*Z*)-**11**, 83845-69-6; **12**, 5682-83-7; **16**, 83915-68-8; $PhCH_2OH$, 100-51-6; *p*-$NO_2C_6H_4CH_2OH$, 619-73-8; $CH_3(CH_2)_6OH$, 111-70-6; $CH_3(CH_2)_9OH$, 112-30-1; $CH_3(CH_2)_3CH(OH)CH_3$, 626-93-7; $CH_3(CH_2)_3CH(OH)C_2H_5$, 589-82-2; *t*-PhCH=$CHCH_2OH$, 4407-36-7; *t*-PhCH=CHCH(OH)Ph, 62668-02-4; PhCH(OH)COPh, 119-53-9; $PhCH(OH)CO_2Et$, 774-40-3; $PhCH(OH)CH_2CO_2Et$, 5764-85-2; PhCH(OH)CH(OH)Ph, 492-70-6; PhCHO, 100-52-7; *p*-$NO_2C_6H_4CHO$, 555-16-8; $CH_3(CH_2)_5CHO$, 111-71-7; $CH_3(CH_2)_8CHO$, 112-31-2; $CH_3(CH_2)_3COCH_3$, 591-78-6; $CH_3(CH_2)_3COC_2H_5$, 106-35-4; *t*-PhCH=CHCHO, 14371-10-9; *t*-PhCH=CHCOPh, 614-47-1; CH_2=$C(SiMe_3)COPh$, 83845-70-9; PhCOCOPh, 134-81-6; $PhCOCO_2Et$, 1603-79-8; *t*-PhCH=$CHCO_2Et$, 4192-77-2; cyclopentanol, 96-41-3; cyclohexanol, 108-93-0; carveol, 99-48-9; cyclopentanone, 120-92-3; cyclohexanone, 108-94-1; carvone, 99-49-0; 1-phenyl-2-(trimethylsilyl)-2-propen-1-ol, 51666-96-7; (α-lithiovinyl)trimethylsilane, 51666-94-5; cyclohexene oxide, 286-20-4; α-lithiobenzyl phenyl selenide, 56253-58-8; *N*-chlorosuccinimide, 128-09-6.

Reaction of Phenylhydroxylamine with Bisulfite. A Possible Model for Amine-Mediated Carcinogenesis

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Under anaerobic conditions, phenylhydroxylamine reacts with the model nucleophile (bi)sulfite to form aniline, *o*- and *p*-aminophenol, and *o*- and *p*-aminobenzenesulfonate. Evidence is presented suggesting that all products result from intermediates formed from nucleophilic attack of both bisulfite and sulfite on the arylhydroxylamine with subsequent covalent addition–elimination processes leading to products. Such a scheme offers a possible alternative pathway for describing the mechanism for carcinogenic arylation of nucleic acid residues by arylhydroxylamines not requiring the intermediacy of short-lived free radicals or nitrenium ions.

In aqueous systems (in the absence of biological materials) at physiological pH, arylhydroxylamines undergo a series of reactions in the presence of O_2, resulting in their conversion to the corresponding 4-nitrosophenol, nitroso, nitro, and azoxy compounds. Under anaerobic conditions at similar pH, the arylhydroxylamine is stable.[5] The

† University of Kansas.
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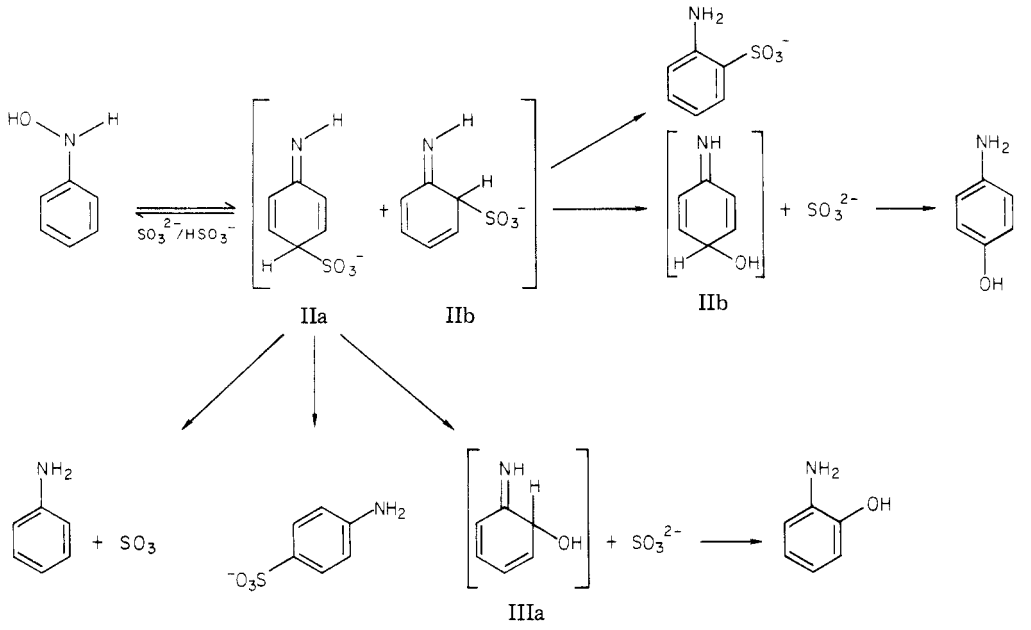
(1) Becker, A. R.; Sternson, L. A. *Proc. Natl. Acad. Sci. U.S.A.* **1981**, *78*, 2003.

0022-3263/83/1948-0057$01.50/0

Scheme I



carcinogenicity of primary aromatic amines is initiated by their oxidation to the corresponding arylhydroxylamine and subsequent arylation of nucleic acid residues.[2,3] In biological systems, esterification of the hydroxylamine has been suggested as prerequisite for expression of mutagenicity, by facilitating expulsion of the hydroxyl moiety to form highly reactive electrophilic nitrenium ion intermediates, which are postulated to be proximal carcinogens[2-5] that subsequently react with relatively week nucleophilic sites on nucleotides. Bisulfite has been suggested[6,7] as being a useful model for studying the covalent addition of nucleophilic groups in enzymes to suitable electrophilic receptor molecules in a variety of biochemical processes. Using this model, we have now found that arylhydroxylamines are also subject to direct nucleophilic attack by (bi)sulfite on the aromatic ring in the absence of oxygen, esterifying agents, or strong acids to yield an intermediate that is activated toward further attack by nucleophiles, offering an alternative mechanism for their arylation of DNA residues.

Phenylhydroxylamine (PhNHOH) dissolved in 0.0025 M phosphate buffer (pH 6.0–8.2) reacts with sodium (bi)sulfite in the absence of O_2 to form aniline, *o*- and *p*-aminophenol, and *o*- and *p*-aminobenzenesulfonate (Scheme I). All products were characterized from their thin-layer and high-pressure liquid chromatographic behavior, mass spectra, which were identical with those of authentic samples, and elemental analyses which were within acceptable limits (±0.4%). The loss of PhNHOH (5×10^{-5} M) from deoxygenated, metal-free, aqueous phosphate buffer solutions (0.0025 M, pH M, pH 6.0–8.2) in the presence of sodium bisulfite ($0.5–2.0 \times 10^{-3}$ M) at 28 °C followed first-order kinetic behavior for a minimum of 5 half-lives, as did the formation of each of the products. The dependence of PhNHOH disappearance on (bi)sulfiate concentration was determined by measuring PhNHOH concentration as a function of time at ≥5 concentrations of (bi)sulfite at each pH studied. Plots of k_{obsd} vs. total (bi)sulfite concentration (S_T) at each pH were linear with zero intercept, indicating a first-order dependence of substrate loss on (bi)sulfite concentration and the lack of a (bi)sulfite-independent term, i.e., confirming the stability of PhNHOH in the absence of HSO_3^- and O_2.[1] The (bi)sulfite-dependent rate constant (k_s) was assumed to consist of an HSO_3^- and SO_3^{2-} component, as described by eq 1. Rearranging eq 1 and expressing HSO_3^- and SO_3^{2-} in terms of total sulfite (S_T) concentration gives eq 2, where K_a is the acid dissociation constant for bisulfite ($K_a = 10^{-7.1}$) and a_H is the activity of H_3O^+. k_s was given by the slope (defined as slope A) of plots of k_{obsd} vs. S_T (eq 1). From k_s calculated at each pH, bisulfite- (k') and

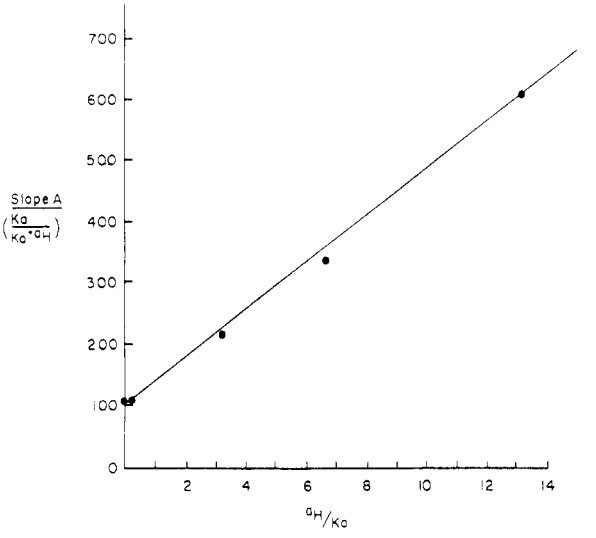


Figure 1. Secondary plot of slope $A/K_a(K_a + a_H)^{-1}$ vs. (a_H/K_a) for reaction of PHA with (bi)sulfite. The theoretical line was computer generated by a least-squares program.

$$v/[\text{PhNHOH}] = k_{obsd} = k_s S_T = k'[HSO_3^-] + k''[SO_3^{2-}] \quad (1)$$

$$k_{obsd} = [k'(a_H/(K_a + a_H)) + k''(K_a/(K_a + a_H))]S_T \quad (2)$$

(2) Kadlubar, F. F.; Miller, J. A.; Miller, E. C.; *Cancer Res.* **1976**, *36*, 1196.
(3) Miller, J. A.; Miller, E. C. *Prog. Exp. Tumor Res.* **1969**, *11*, 273.
(4) Lotlikar, P. D.; Scribner, J. D.; Miller, J. A.; Miller, E. C. *Life Sci.* **1966**, *5*, 1263.
(5) Miller, E.; Juhl, U.; Miller, J. A. *Science (Washington, D.C.)* **1966**, *153*, 1125.
(6) Triplett, J. W.; Smith, S. L.; Layton, W. J.; Digenis, G. A. *J. Med. Chem.* **1977**, *20*, 1594.
(7) Pitman, I. H.; Jain, N. B. *Aust. J. Chem.* **1979**, *32*, 545.

Table I. Product Distribution[a,b] (%)

$[NaHSO_3]_T$, M	PAS[d]	OABS[d]	PAP[d]	OAP[d]	$PhNH_2$[d]	total yield
			pH 6[c]			
5.0×10^{-4}	17.5 ± 1.2	16.6 ± 1.0	30.8 ± 2.5	5.8 ± 0.8	22.9 ± 0.9	93.6
1.0×10^{-3}	17.7 ± 3.7	16.8 ± 0.6	31.7 ± 2.7	6.2 ± 0.5	21.8 ± 0.7	94.2
1.6×10^{-3}	16.8 ± 0.9	16.3 ±1.1	33.9 ± 8.4	8.4 ± 1.2	17.1 ± 1.0	92.5
2.0×10^{-3}	22.8 ± 0.8	17.0 ± 0.9	28.8 ± 1.9	6.7 ± 1.8	21.3 ± 1.2	96.6
			pH 6.3			
5.0×10^{-4}	16.4 ± 1.6	13.7 ± 0.7	35.8 ± 1.0	8.1 ± 0.5	24.7 ± 1.7	98.7
1.0×10^{-3}	18.7 ± 0.4	15.1 ± 1.9	34.4 ± 0.9	8.7 ± 1.8	21.7 ± 2.3	98.6
1.5×10^{-3}	20.0 ± 0.8	17.7 ± 1.3	34.7 ± 1.1	8.4 ± 3.1	17.9 ± 1.6	98.7
2.0×10^{-2}	21.4 ± 1.2	18.4 ± 0.8	31.2 ± 0.6	9.1 ± 2.6	20.6 ± 0.9	100.7
			pH 6.6			
5.0×10^{-4}	18.1 ± 0.4	11.8 ± 0.9	32.5 ± 1.7	4.8 ± 0.3	21.3 ± 1.2	88.5
1.0×10^{-3}	18.8 ± 1.1	13.3 ± 1.4	31.7 ± 0.6	5.1 ± 0.7	23.5 ± 0.9	92.4
1.5×10^{-3}	19.7 ± 0.7	12.4 ± 1.5	29.4 ± 0.8	5.2 ± 1.8	20.9 ± 2.0	87.6
2.0×10^{-3}	19.7 ± 2.0	15.1 ± 0.7	29.6 ± 1.1	4.7 ± 1.2	22.4 ± 1.2	91.5
			pH 7.7			
5.0×10^{-4}	16.1 ± 0.6	11.1 ± 0.8	32.5 ± 1.4	6.5 ± 0.9	19.3 ± 1.0	85.5
1.0×10^{-3}	19.0 ± 0.9	12.4 ± 1.0	32.7 ± 3.1	5.9 ± 1.4	15.4 ± 0.8	85.4
1.5×10^{-3}	24.3 ± 0.7	15.4 ± 0.6	27.8 ± 1.7	6.3 ± 2.7	20.1 ± 0.4	93.9
2.0×10^{-3}	26.2 ± 2.0	14.0 ± 0.2	27.1 ± 0.1	4.6 ± 1.2	20.7 ± 5.1	92.6
			pH 8.2			
5.0×10^{-4}	22.3 ± 3.1	15.5 ± 2.6	30.1 ± 1.2	7.7 ± 1.1	23.2 ± 3.0	98.8
1.0×10^{-3}	24.1 ± 0.3	15.9 ± 0.4	29.8 ± 0.3	6.8 ± 1.8	17.6 ± 0.9	94.2
1.5×10^{-3}	26.2 ± 2.0	15.9 ± 0.6	29.3 ± 1.6	6.9 ± 1.3	20.6 ± 0.5	98.9
2.0×10^{-3}	25.1 ± 0.6	15.6 ± 0.1	30.9 ± 1.8	5.4 ± 2.3	22.8 ± 0.5	99.8

[a] Yield determined by HPLC after incubation at 28 °C for 7 half-lives. [b] Yields represent the average ± standard deviation for ≥4 determinations. [c] 0.0025 M phosphate buffer (made metal-free by extraction with dithizone) maintained at μ = 0.5 with sodium perchlorate. [d] PAS = *p*-aminobenzenesulfonate, OABS = *o*-aminobenzenesulfonate, PAP = *p*-aminophenol, OAP = *o*-aminophenol, $PhNH_2$ = aniline.

sulfite- (k'') dependent rate constants could be determined graphically from secondary plots according to eq 3 (Figure

$$\text{slope } A/(K_a/(K_a + a_H)) = k'' + k'(a_H/K_a) \quad (3)$$

1), which gave a straight line with positive intercept. This treatment of the data supports the hypothesis of participation of both HSO_3^- ($k' = 40.5\ M^{-1}\ s^{-1}$) and SO_3^{2-} ($k'' = 102.8\ M^{-1}\ s^{-1}$) in PhNHOH degradation. Similarly, Pitman and Ziser[8] report that both bisulfite and sulfite act as attacking nucleophiles in addition to pyrimidines. The observed similarity in nucleophilic character of bisulfite and sulfite in reaction with PhNHOH and pyrimidines[8] is consistent with the expression of nucleophilicity in terms of the electrode potential (E_n) for the oxidation of the nucleophile (normalized to $E_n = 0$ for Nu = H_2O)[9] since sulfite and bisulfite both exhibit an $E_{1/2} \sim +0.01$ V (vs. SCE).[10] Miller[11] and Pearson[12] have similarly shown that for reactions at other "soft" electrophilic centers, there is no correlation between nucleophilicity and the strength of the nucleophile as a proton base; rather nucleophilicity is governed by the polarizability of the attacking species. In contrast, the rate-determining step in addition to aldehydes and ketones only involves the attack of sulfite on the neutral carbonyl compound.[13] The carbonyl electrophilic center is "harder" (i.e., resembling the proton), and as a result a Brønsted relationship is obeyed for addition to aldehydes and ketones, making any contribution of bisulfite (10^5 times weaker base than SO_3^{2-}) to the carbonyl reaction negligible.

The data presented are readily interpreted in terms of Scheme I, suggesting that PhNHOH may react directly with sulfite to form II, which by proton migration yields the aminosulfonates, through an addition (H_2O)–elimination (SO_3^{2-}) process forms the aminophenols, and by an addition (H_3O^+)–elimination (sulfur trioxide) reaction is reduced to aniline. Bisulfite and sulfite undergo similar reversible covalent addition–elimination reactions with uracils and 5-halouracils[14-18] and with thiamine.[19,20] A mechanism analogous to that proposed to rationalize the formation of aminophenols and aniline was postulated by Bruice in processes in which amines acting as nucleophilic catalysts participate in addition–elimination reactions promoting dienone–phenol rearrangement[21] and aromatization of arene oxides.[22] The intermediacy of a sulfite-addition product (II) leading to the formation of aniline and the aminophenols is further supported by (1) the requirement for (bi)sulfite to initiate anaerobic degradation of PhNHOH, (2) the observed stability of the reaction products (under the experimental conditions used in these

(8) Pitman, I. H.; Ziser, M. A. *J. Pharm. Sci.* **1970**, *59*, 1295.
(9) Edwards, J. O. *J. Am. Chem. Soc.* **1954**, *76*, 1540.
(10) Sawyer, D. T.; Roberts, J. L. "Experimental Electrochemistry for Chemists"; Wiley: New York, 1974; p 371. Sternson, L. A., unpublished results.
(11) Miller, J. *J. Am. Chem. Soc.* **1963**, *85*, 1628.
(12) Pearson, R. G.; Sobel, H.; Songstad, J. *J. Am. Chem. Soc.* **1968**, *90*, 319.
(13) Bishop, C. A.; Porter, R. F. *tong*, K. K. J. *J. Am. Chem. Soc.* **1963**, *85*, 399.
(14) Rork, G. S.; Pitman, I. H. *J. Am. Chem. Soc.* **1974**, *96*, 4654.
(15) Rork, G. S.; Pitman, I. H. *J. Am. Chem. Soc.* **1975**, *97*, 5559.
(16) Rork, G. S.; Pitman, I. H. *J. Am. Chem. Soc.* **1975**, *97*, 5566.
(17) Shapiro, R.; Servis, R. E.; Welcher, M. *J. Am. Chem. Soc.* **1970**, *92*, 422.
(18) Sedor, F.; Jacobson, D. G.; Sander, E. G. *Bioorg. Chem.* **1974**, *3*, 221.
(19) Zoltewicz, J. A.; Kauffman, G. M. *J. Am. Chem. Soc.* **1977**, *99*, 3134.
(20) Doerge, D. R.; Ingraham, L. L. *J. Am. Chem. Soc.* **1980**, *102*, 4028.
(21) Becker, A. R.; Richardson, D. J.; Bruice, T. C. *J. Am. Chem. Soc.* **1977**, *99*, 5058.
(22) Johnson, D. M.; Bruice, T. C. *J. Am. Chem. Soc.* **1975**, *97*, 6901.
(23) Smissman, E. E.; Corbett, M. D. *J. Org. Chem.* **1972**, *37*, 1847.
(24) Thiers, R. E. "Methods of Biochemical Analysis"; Glick, O., Ed.; Interscience: New York, 1955, Vol. V, pp. 273.

studies), and (3) the observed trends in product distribution.

Product distribution was essentially independent of pH and (bi) sulfite concentration over the range studied (pH 6.0–8.2; S_T = (0.5–2.0) × 10^{-3} M; Table I) as determined by HPLC after incubation of PhNHOH at 28 °C with (bi)sulfite in deoxygenated phosphate buffer (0.0025 M) for at least 7 half-lives. The low relative yield of *o*-aminophenol may arise from steric restriction of attack by water at the ortho position of IIa to form an intermediate, IIIa, of apparent greater steric strain than its precursor. Similarly, the relatively high yield of *p*-aminophenol may reflect relief of steric strain in IIb following attack by water to form IIIb. In all cases *p*-aminobenzenesulfonate was formed in greater yield than *o*-aminobenzenesulfonate, again reflecting steric resistance to attack at the ortho sites.

This reactivity of PhNHOH toward the strong nucleophile (bi)sulfite suggests that, in some cases, arylhydroxylamine-mediated carcinogenesis may involve direct nucleophilic aromatic attack by a strong endogenous nucleophile with concerted expulsion of hydroxide, to form an intermediate that can either rearrange to form a stable product or undergo a further nucleophilic addition reaction (even with relatively weak nucleophilic species; i.e., H_2O in the study described above) followed by elimination involving formation of potentially mutagenic species. Such a scheme offers a possible alternative mechanism for arylation of endogenous materials by arylhydroxylamines not requiring the intermediacy of short-lived free radicals or nitrenium ions and now requires further investigation in more biochemically relevant systems.

Experimental Section

Phenylhydroxylamine was synthesized by reduction of nitrobenzene with zinc and ammonium chloride.[23] All buffers were demetalated by extraction with dithizone as previously described.[24]

Kinetic studies were carried out at 28 ± 0.5 °C by incubating PhNHOH in deoxygenated 0.0025 M phosphate buffer maintained at a constant ionic strength (μ = 0.5) with sodium perchlorate in the presence of sodium (bi)sulfite ((0.5–2.0) × 10^{-3} M).

Samples were taken at timed intervals for a minimum of 5 half-lives and analyzed by HPLC. Components were separated on a Waters μBondapak C_{18} column (30 cm × 4.6 mm i.d.) by using a mobile phase of methanol:water (15:85) containing 0.26 M NH_4(OAc) and 0.015 M nickel acetate. A flow rate of 2 mL min^{-1} was maintained and effluent monitored spectrophotometrically at 254 nm. Retention volumes for *p*-aminobenzenesulfonate, o-aminobenzenesulfonate, *p*-aminophenol, *o*-aminophenol, phenylhydroxylamine, and aniline were 3, 4.4, 5, 9.0, 9.9, and 13.1 mL, respectively.

Product distribution was determined by HPLC after incubation for ≥7 half lives.

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Registry No. PhNHOH, 100-65-2; aniline, 62-53-3; *o*-aminophenol, 95-55-6; *p*-aminophenol, 123-30-8; *o*-aminobenzenesulfonate, 88-21-1; *p*-aminobenzenesulfonate, 121-57-3.

Ramberg–Bäcklund Reaction of 1,3-Dibromo-1*H*,3*H*-naphtho[1,8-*cd*]thiopyran 2,2-Dioxide. Formation of Acenaphthyne Intermediate

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Radical bromination of 1*H*,3*H*-naphtho[1,8-*cd*]thiopyran 2,2-dioxide (**15**) gave the corresponding monobromo sulfone **16** (48%), dibromo sulfone **12** (43%; cis/trans = 64/36), and tribromo sulfone **17** (5%). Ramberg–Bäcklund reaction of **12** was investigated under a variety of conditions with expectation of the formation of thiirene dioxide **11** from which generation of acenaphthyne (**5**) would be expected both thermally and photochemically. Observed characteristic features of the reaction are as follows: (i) the use of triethylamine as base yielded 1-bromoacenaphthylene (**20**; 39%) and debrominated products **15** (5%) and **16** (9%); (ii) the use of sodium methoxide as base afforded decacyclene (**3**) surprisingly, though in a trace amount, in addition to **20** (75%) and acenaphthylene (**18**; 9%); (iii) the use of potassium *tert*-butoxide as base gave an improved yield of **3** (5%) along with **20** (36%) and **18** (27%). The formation of **3** may best be rationalized by assuming the generation of acenaphthyne intermediate **5** from **11** by loss of sulfur dioxide.

We have previously shown that thermolysis of the potassium salt of acenaphthenequinone bis(tosylhydrazone) (**1**, Scheme I) in solution yields 1,8-dicyanonaphthalene (**2**) and decacyclene (**3**).[1] The result may best be explained by the initial formation of a bis(diazo) compound or its ring-closed isomer **4**, which either gives **2** with loss of one molecule of nitrogen or yields acenaphthyne (1,2-dehydroacenaphthylene, **5**) with loss of two molecules of nitrogen, and then **5** results in the formation of **3**. The purpose of the present study is to generate **5** by another method in order to establish the true existence of this highly strained molecule as an intermediate.

The most strained cycloalkyne, whose existence was convincingly established, is norbornyne (bicyclo[2.2.1]-hept-2-yne, **6**).[2,3] 2-Lithio-1-chlorobicyclo[2.2.1]hept-2-ene

(1) Nakayama, J.; Segiri, T.; Ohya, R.; Hoshino, M. *J. Chem. Soc., Chem. Commun.* **1980**, 791–792.

(2) (a) Gassman, P. G.; Valcho, J. J. *J. Am. Chem. Soc.* **1975**, *97*, 4768–4770. (b) Gassman, P. G.; Gennick, I. *Ibid.* **1980**, *102*, 6863–6864.

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