a foam, which was chromatographed on a silica gel column with chloroform–methanol (100:1, then 60:1) to give **3** as a foam (4.84 g, 97%): ^{1}H NMR ($CDCl_3$) δ 0.13 [s, 6 H, $Si(CH_3)_2$], 0.93 [s, 9 H, $SiC(CH_3)_3$], 2.54 (m, 2 H, H-2′), 4.00 (s, 2 H, H-5′), 4.42 (s, 1 H, H-4′), 5.74 (apparent d, 2 H, H-5 and H-3′), 6.50 (dd, 1 H, J = 5.5 and 8.5 Hz, H-1′), 6.97–7.57 (m, 5 H, C_6H_5), 7.93 (d, 1 H, J = 8.2 Hz, H-6), 9.35 (br s, 1 H, NH). Anal. Calcd for $C_{22}H_{30}N_2O_6SSi$: C, 55.21; H, 6.32; N, 5.85. Found: C, 55.46; H, 6.45; N, 5.83.

5′-*O*-(*tert*-Butyldimethylsilyl)-3′-*O*-(phenoxythiocarbonyl)thymidine (4). 5′-*O*-(*tert*-Butyldimethylsilyl)thymidine **2** (3.56 g, 10 mmol) in methylene chloride (25 mL) and pyridine (6 mL) was stirred with phenyl chlorothionoformate (5.0 g, 29 mmol) at 0 °C for 1 h and then left overnight in the refrigerator. The solvents were evaporated in vacuo, and the residue was suspended in water and extracted with chloroform. After evaporation of the chloroform, the residue was chromatographed on a silica gel column with chloroform–methanol (60:1) as the eluent to give **4** (4.29 g, 87%); mp 167–169 °C (ether); ^{1}H NMR (Me_2SO-d_6) δ ~0.0 [s, 6 H, Si $(CH_3)_2$], 0.78 [s, 9 H, $SiC(CH_3)_3$], 1.69 (s, 3 H, C_5-CH_3), 1.88–2.64 (m, 2 H, H-2′), 3.80 (d, 2 H, J = 2.0 Hz, H-5′), 4.24 (br s, 1 H, H-4′), 5.60 (d, 1 H, J = 3.7 Hz, H-3′), 6.22 (dd, 1 H, J = 4.8 and 6.5 Hz, H-1′), 6.99–7.50 (m, 6 H, C_6H_5 and H-6), 11.29 (br s, 1 H, NH). Anal. Calcd for $C_{23}H_{32}N_2O_6SSi$: C, 56.07; H, 6.55; N, 5.69. Found: C, 56.16; H, 6.60; N, 5.68.

5′-*O*-(*tert*-Butyldimethylsilyl)-3′-*C*-allyl-2′,3′-dideoxyuridine (5). A mixture of **3** (0.65 g, 1.36 mmol), allytributyltin (0.84 mL, 2.72 mmol), and azobisisobutyronitrile (AIBN) (0.037 g, 0.272 mmol) in toluene (10 mL) was heated at 78–83 °C for 24 h. Additional AIBN (0.03 g) was added, and the heating was continued for 4 more days. Evaporation of the solvent and chromatography on a silica gel column with hexanes–ethyl acetate (3:2) yielded **5** as a syrup (0.249 g, 50%): UV (MeOH) λ_{max} (pH 6) 264 (ϵ 9240), (pH 1) 264 (ϵ 9930), (pH 11) 263 (ϵ 7340); ^{1}H NMR ($CDCl_3$) δ 0.11 [s, 6 H, $Si(CH_3)_2$], 0.93 [s, 9 H, $SiC(CH_3)_3$], 1.90–2.45 (m, 5 H, H-2′, H-3′, and CH_2), 3.62–4.18 (m, 3 H, H-4′ and H-5′), 5.64 (d, 1 H, H-5), 4.90–5.21 and 5.49–5.92 (2 m, 3 H, $CH{=}CH_2$), 6.07 (dd, 1 H, J = 4.1 and 4.8 Hz, H-1′), 8.13 (d, 1 H, J = 7.9 Hz, H-6), 9.48 (br s, 1 H, NH). Anal. Calcd for $C_{18}H_{30}N_2O_4Si$: C, 58.98; H, 8.25; N, 7.64. Found: C, 59.10; H, 8.29; N, 7.57.

5′-*O*-(*tert*-Butyldimethylsilyl)-3′-*C*-allyl-2′,3′-dideoxythymidine (6). A mixture of **4** (0.69 g, 1.4 mmol), allyltributyltin (2.5 mL, 8.07 mmol), and AIBN (0.037 g, 0.272 mmol) in toluene (5 mL) was heated at 80 °C for 15 h. Another portion of AIBN (0.040 g) was added gradually over a period of 8 h, and the heating was continued for 2 days. The solvent was evaporated in vacuo, and the residue was chromatographed on a silica gel column with hexane–ethyl acetate (7:3) as the eluent to obtain the major fraction **6** (0.395 g, 74%): mp 114–115 °C (hexanes–ether); UV (MeOH) λmax (pH 7) 268 (ϵ 10550), (pH 1) 268.5 (ϵ 10415), (pH 11) 268.5 (ϵ 8440); ^{1}H NMR (Me_2SO-d_6) δ 0.12 [s, 6 H, $Si(CH_3)_2$], 0.94 [s, 9 H, $SiC(CH_3)_3$], 1.92 (s, 3 H, 5-CH_3), 1.70–2.53 (m, 5 H, H-2′, H-3′, and CH_2), 3.57–4.14 (m, 3 H, H-4′, H-5′), 4.86–5.22 and 5.50–6.02 (2 m, 3 H, $CH{=}CH_2$), 6.11 (t, 1 H, J = 3.4 Hz, H-1′), 7.59 (s, 1 H, H-6), 9.87 (s, 1 H, NH). Anal. Calcd for $C_{19}H_{32}N_2O_4Si$: C, 59.97; H, 8.47; N, 7.36. Found: C, 59.98; H, 8.51; N, 7.35.

3′-*C*-Allyl-2′,3′-dideoxyuridine or 3′-(2-Propen-1-yl)-2′,3′-dideoxyuridine (7). A mixture of **5** (0.249 g, 0.69 mmol) and tetrabutylammonium fluoride (1.5 mL, 1 M solution in THF) in THF (5 mL) was stirred for 3 h. After the removal of the solvent in vacuo, the residue was chromatographed on a silica gel column with chloroform–methanol (22:1) as the eluent to obtain **7** (0.13 g, 76%): mp 137–138 °C (chloroform–ether); UV (MeOH) λmax (pH 6) 263.5 (ϵ 10780), (pH 1) 263.5 (ϵ 11215), (pH 11) 263 (ϵ 7900); ^{1}H NMR (Me_2SO-d_6, 500 MHz) δ 2.06 (m, 2 H, $J_{2',3'}$ = 3.3 Hz, $J_{2',1'}$ = 6.9 Hz, H-2′), 2.07 (m, 1 H, H-3′), 2.24 (m, 1 H, $J_{6'b,8'a}$ = 4.2 Hz, H-6′b), 2.32 (m, 1 H, $J_{6'a,7'}$ = 2.8 Hz, H-6′a), 3.33 (s, 1 H, OH exchangeable), 3.51 (dt, 1 H, $J_{8'a,7'}$ = 11.9 Hz, H-8′a), 3.64 (dt, 1 H, $J_{8'b,7}$ = 8.3 Hz, $J_{8'b,6'a}$ = 2.8 Hz, H-8′b), 3.75 (dq, 1 H, $J_{7',8'a}$ = 11.9 Hz, H-7′), 5.06 (m, 2 H, H-5′), 5.58 (d, 1 H, $J_{5,6}$ = 7.1 Hz, H-5), 5.80 (m, 1 H, H-4′), 5.97 (q, 1 H, $J_{1',2'}$ = 6.9 Hz, H-1′), 8.02 (d, 1 H, $J_{6,5}$ = 7.1 Hz, H-6), 11.23 (s, 1 H, NH exchangeable). Anal. Calcd for $C_{12}H_{16}N_2O_4$: C, 57.13; H, 6.39; N, 11.10. Found: C, 56.96; H, 6.41; N, 11.02.

3′-*C*-Allyl-2′,3′-dideoxythymidine or 3′-(2-Propen-1-yl)-2′,3′-dideoxythymidine (8). A mixture of **6** (0.27 g, 0.7 mmol) and tetrabutylammonium fluoride (2 mL, 1 M solution in THF) in THF (10 mL) was stirred at 0 °C for 3 h. The product having R_f 0.35 (chloroform–methanol, 25:1) was isolated by a silica gel column with the above solvent mixture as the eluent to give **8** (0.145 g, 77%) as a syrup: UV (MeOH) λmax (pH 7) 268 (ϵ 7760), (pH 1) 269 (ϵ 7610), (pH 11) 268 (ϵ 6410); ^{1}H NMR (Me_2SO-d_6, 500 MHz) δ 1.76 (s, 3 H, $J_{5,6}$ = 1.0 Hz, CH_3), 2.02 (m, 1 H, $J_{2'a,2'b}$ = 2.1 Hz, $J_{2'a,1'}$ = 6.9 Hz, H-2′a), 2.04 (m, 1 H, $J_{2'b,2'a}$ = 2.1 Hz, $J_{2'b,1'}$ = 3.5 Hz, H-2′b), 2.08 (m, 1 H, $J_{3',4'}$ = 7.8 Hz, $J_{3',6'}$ = 9.3 Hz, H-3′), 2.24 (m, 1 H, $J_{6'b,6'a}$ = 7.1 Hz, $J_{6'b,8'b}$ = 1.1 Hz, H-6′b), 2.31 (m, 1 H, $J_{6'a,7'}$ = 6.1 Hz, H-6′a), 3.56 (dq, 1 H, $J_{8'b,7'}$ = 12.1 Hz, $J_{8'b,8'a}$ = 3.7 Hz, H-8′b), 3.63 (dt, 1 H, $J_{8'a,7'}$ = 2.7 Hz, H-8′a), 3.75 (dq, 1 H, $J_{7',8'a}$ = 2.7 Hz, $J_{7',6'a}$ = 6.1 Hz, H-7′), 5.01 (m, 1 H, $J_{5'a,5'b}$ = 1.8 Hz, $J_{5'a,4'}$ = 10.2 Hz, H-5′a), 5.07 (s, 1 H, OH exchangeable), 5.09 (m, 1 H, $J_{5'b,4'}$ = 10.2 Hz, H-5′b), 5.78 (m, 1 H, $J_{4',5'a}$ = 10.2 Hz, $J_{4',3'}$ = 7.9 Hz, H-4′) 5.96 (dd, 1 H, $J_{1',2'a}$ = 6.9 Hz, $J_{1',2'b}$ = 3.5 Hz, H-1′), 7.87 (d, 1 H, $J_{6,5}$ = 1.0 Hz, H-6), 11.20 (s, 1 H, NH, exchangeable). Anal. Calcd for $C_{13}H_{18}N_2O_4$: C, 58.66; H, 6.77; N, 10.52. Found: C, 58.38; H, 6.79; N, 10.47.

Diffraction Analysis of 7. The sample was recrystallized by slow evaporation of an aqueous ethyl acetate solution. The crystal used had approximate dimensions of 0.12 × 0.60 × 0.65 mm. The crystal belongs to the monoclinic space group $P2_1$ with cell dimensions a = 14.490 (1) Å, b = 8.338 (1) Å, c = 5.199 (1) Å, β = 99.375 (7)°, V = 619.70 (9) Å^3, Z = 2. The intensity data were measured on a Nicolet P3 diffractometer using Nb-filtered Mo Kα radiation (λ = 0.71069 Å). A total of 1362 of the 1474 unique data measured had $F > 3\sigma(F)$ and were considered observed. The structure was refined by full-matrix least-squares methods. Hydrogen atom positions were determined from difference maps and included in the refinement after the refinement of the nonhydrogen atoms had convered.

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Supplementary Material Available: Atomic coordinates and anisotropic thermal parameters (2 pages); observed and calculated structure factor amplitudes (10 pages). Ordering information is given on any current masthead page.

Ambident Nucleophilicity of Silver Hyponitrite toward Organic Halides

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Organic esters of *trans*-hyponitrous acid are useful sources of alkoxyl radicals for a wide range of theoretical and practical applications.[1] The reaction of silver hyponitrite with alkyl halides is the oldest and most universal synthesis of these esters:[1,2]

$$2RX + \underset{\mathbf{I}}{Ag_2N_2O_2}(s) \rightarrow 2AgX(s) + RON{=}NOR \quad (1)$$

R = organic group; X = Cl, Br, I

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The low yields that are frequently obtained from reaction 1 often can be explained by the slowness of the reaction and the instability of the organic products. In addition, we have inferred the presence of side reactions, based on (a) development of a strong odor of cyclohexene in mixtures of cyclohexyl bromide and silver hyponitrite and (b) isolation of ill-defined, thermally stable products from attempts to carry out reaction 1 with benzylic halides derived from naphthalene or anthracene.[3]

When benzhydryl chloride reacted with 1 in benzene–hexanes, a colorless, stable product was isolated in low yield. The combustion analysis and spectral data were consistent with hyponitrite isomer **2**. The new compound showed two narrow methine singlets of equal height in its proton NMR spectrum, and, in contrast to the labile **3** (calcd[4] $t_{1/2}$ = 2.4 h at 25 °C), the spectrum was unchanged on standing or heating. Diazene *N*-oxides with organic groups different from those in **2** have been synthesized by other methods and are also thermally stable.[5] When benzhydryl hyponitrite **3** was allowed to decompose in $CDCl_3$ or other solvents, no **2** could be detected by ^1H NMR spectroscopy.

$$2Ph_2CHCl + Ag_2N_2O_2 \xrightarrow{C_6H_6\text{–}C_6H_{14}} Ph_2CHON{=}\overset{+}{N}(O)\overset{-}{C}HPh_2$$

2

$$2Ph_2CHBr + Ag_2N_2O_2 \xrightarrow{CH_2Cl_2} Ph_2CHON{=}NOCHPh_2$$

3

Examination of the reaction products from 1 and benzhydryl halides was conveniently carried out by ^1H NMR spectroscopy, since the methine resonances are unique for starting materials and products. In benzene–hexanes benzhydryl chloride gave only **2**, in CH_2Cl_2 a 3:1 mixture of **2** and **3** was obtained, and in acetonitrile and in hexanes no reaction was observed.

With benzhydryl bromide in methylene chloride, reaction 1 proceeded very cleanly to give a solution that displayed a methine signal only for **3**. The same reaction in acetonitrile gave a solution whose proton NMR spectrum displayed four methine signals in a 1:1:2:2 ratio. They were ascribed, respectively, to **2**, benzhydrol (^1H NMR at δ 5.8, signal enhanced with authentic sample), and benzhydryl ether (δ 5.42, lit.[6] δ 5.45). In 2:1 benzene–hexanes the same reaction gave a solution on workup that showed a large signal at δ 5.42, while signals from **2** and **3** were absent. In hexanes no reaction was observed. Resonances from benzhydryl peroxide (lit[7] δ 6.10) were absent from reaction mixtures of either halide.

The speed of reaction 1 depends greatly on the nature of the halide. In order to characterize this effect more fully, we introduced samples of silver hyponitrite in one portion into stirred halides in an insulated container and recorded the temperature with time. The strongly exothermic reaction of silver hyponitrite with *tert*-butyl bromide has been described.[2] Benzhydryl chloride and allyl bromide also reacted instantly with **1**, whereas isopropyl bromide did so after an induction period. (We have also observed induction periods in the reaction with cyclohexyl bromide.)

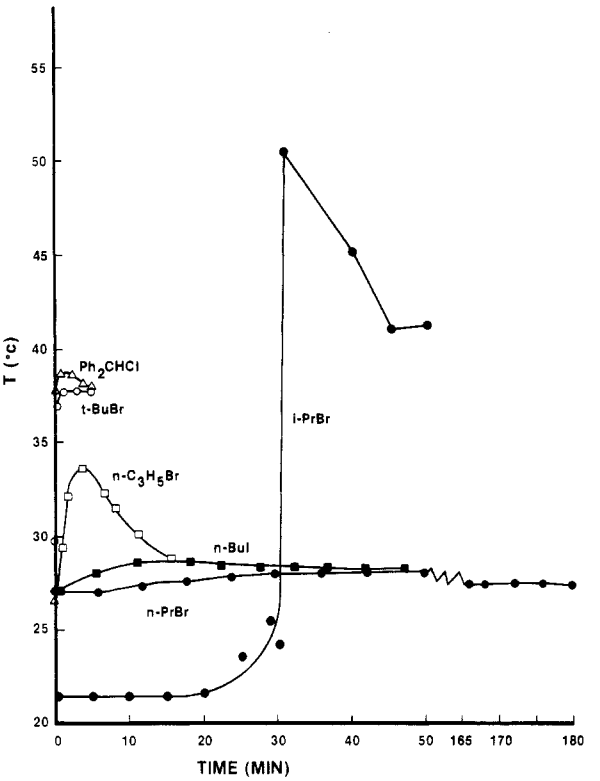

Figure 1. Reaction 1 followed by the temperature of magnetically stirred mixtures. The quantities of **1** and neat RX were respectively 2.7 g and 11 mL for i-PrBr, 0.33 g and 3.3 mL for *n*-PrBr, and 0.5 g and 5 mL for the others.

The corresponding reactions with two primary halides produced a barely perceptible rise in temperature, and in synthetic practice they are carried out at subambient temperatures for extended periods.[1a,4] Although the organic halides were not present in equal amounts nor concentrations in all reactions studied, the apparent reactivities of **1** in this series roughly correspond to the expected ease of formation of the respective organic cations from the halides.

Allyl hyponitrite has been mentioned in the patent literature[8] and was characterized in this work as a lachrymatory and shock-sensitive liquid that could be stored unchanged for extended periods at −16 °C. The ^1H NMR spectrum of the filtered and concentrated reaction mixture of **1** and allyl bromide did not show any signals that could be ascribed to an isomeric hyponitrite analogous to **2**.

Dry sodium hyponitrite does not react with *tert*-butyl bromide. This observation, the order of reactivities with organic structure described above, and the induction period that was observed with i-PrBr (Figure 1) are all consistent with a mechanism for reaction 1 involving cation-assisted nucleophilic displacement. The displacement is catalyzed with secondary bromides by the freshly precipitated silver halide.[9] Our experience that reaction 1 is strongly inhibited if the silver hyponitrite is not thoroughly dry is of course also consistent with this mechanism. A possible explanation for the failure of reaction 1 to occur under some conditions is that the solvent must be polar enough to stabilize reactive intermediates but not so polar that it is bound to **1** more strongly than the halide.

The distribution of the reaction products between **2** and **3** is interesting, but we are reluctant to advance reasons

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for this behavior because it is not clear at which stage the unusual N-alkylation occurs. The nitrogen-free products from 1 and benzhydryl halides, on the other hand, presumably arose via decomposition of 3 or of an intermediate RON=NOAg. Finally, we have confirmed the presence of an elimination process by detecting cyclohexene in reaction mixtures of 1 and cyclohexyl bromide.

Experimental Section

Silver hyponitrite, precipitated from 1% solutions of the sodium salt at pH 7-8 (acetate buffer) with dilute silver nitrate, was dried below 1 Torr in an Al foil wrapped container and stored at -16 °C. The samples were redried in the same way for at least 30 min just before use. Solvents were reagent grade, and the halides were obtained from commercial sources and were usually redistilled or recrystallized before use. The analysis was performed by Spang Microanalytical Laboratory, Eagle Harbor, MI. NMR spectra (referenced to TMS) were recorded with a Varian EMI360 or XL-200 instrument and IR spectra with a PE Model 283B or a Nicolet Model 7199 spectrometer. Gas chromatography was carried out with an HP Model 5880 instrument and a 50 m × 0.2 mm i.d. capillary column (PONA, HP Cat. No. 19091S).

***N*-(Diphenylmethoxy)-*N'*-(diphenylmethyl)diazene *N'*-Oxide (2).** Chlorodiphenylmethane (2.05 g, 10 mmol) was dissolved in 10 mL of 2:1 benzene–mixed hexanes with stirring. Silver hyponitrite (2.74 g, 10 mmol, excess to minimize unreacted halide) was added slowly at room temperature, and the mixture was stirred magnetically for 3.5 h. The solution was filtered, and the filtrate was cooled in a liquid nitrogen–acetone slush bath. The resulting white crystals were recrystallized from methanol to give 11% yield of the product; mp 131-133 °C. IR (Nujol): 2840-2980 (br), 1480 (m), 1450 (s), 1375 (s), 1264 (w), 1285 (w), 1025 (s), 1000 (s), 940 (w), 910 (w), 800 (m), 755 (s), 740 (s), 695 (s), 660 (m), 600 (s), 565 (m), 555 (s), cm^{-1}. The ^1H NMR spectrum in $CDCl_3$ showed 1:1 singlets at δ 6.39 and 6.50 and an aromatic peak at δ 7.01-7.50. Anal. Calcd for $C_{26}H_{22}N_2O_2$: C, 79.19; H, 5.58; N, 7.11. Found: C, 79.14; H, 5.53; N, 7.12.

Isolation of the hyponitrite 3 has been described elsewhere.[4] The reactions in various solvents for the product study by ^1H NMR spectroscopy were conducted on a smaller scale in a manner similar to the syntheses of 2, with a stoichiometric excess of 1 added to the halide dissolved in 6-8 times its weight of solvent at 0 °C. After being stirred at 0 °C for about 20 min and at room temperature until no further changes in the appearance of the solid phase were evident, the mixture was filtered or centrifuged, the AgX was washed with the solvent of reaction, and the combined filtrate and washings were concentrated under reduced pressure. The residue was dissolved in $CDCl_3$, and the spectrum was recorded.

Allyl hyponitrite was prepared by addition of 0.2 g (0.7 mmol) of 1 to 2 mL of allyl bromide stirred in an ice bath. After 1 h the ice had melted, and the mixture was filtered and then concentrated with appropriate precautions to ca. 0.1 g of a shock-sensitive liquid that was stable for days at -16 °C. ^1H NMR ($CDCl_3$): δ 4.73 (d of mlt, J = 5 Hz, 2 H), 5.3 (mlt, 2 H), 6.0 (mlt, 1 H). After standing overnight at room temperature, a varnishlike deposit had formed on the inner wall of the NMR tube beneath the liquid level. The spectrum was again recorded, and revealed a new multiplet centered at δ 3.5 whose position and fine structure matched those of the CH_2 group of authentic allyl alcohol in $CDCl_3$. Acrolein, the other anticipated product, is known to polymerize in the presence of free-radical initiators.[10] IR (ν, neat): 3079 (w), 2930 (m), 1733 (w), 1636 (w), 1428 (s), 1339 (m), 1205 (m), 1019 (vs), 922 (vs), 684 (m). MS: m/z (relative intensity) 143 (0.2), 142 (0.3), 141 (1.5), 125 (1.4), 120 (0.2), 112 (6.2), 88 (12.5), 85 (5.0), 82 (4.0), 81 (8), 57 (14), 55 (23), 54 (15), 42 (8), 41 (100).

Cyclohexene from 1 and Cyclohexyl Bromide. A solution of the bromide (815 mg, 5.00 mmol) in hexanes (10 mL) was treated with 1 (689 mg, 2.50 mmol) at 0 °C, followed by stirring at 25 °C for a total of 5 h. The mixture was filtered, and the filtrate was diluted to 25 mL with hexanes. Gas chromatography (column) revealed a peak with the same retention time as cyclohexene. An olefin signal in the ^1H NMR spectrum of the solution at δ 5.65 was enhanced upon addition of authentic cyclohexene. The yield was determined as 34% (based on halide) by comparison of the GC peak area with that from a standard solution of the olefin.

Measurements shown in Figure 1 were carried out with magnetically stirred samples in small, serum-capped round-bottom flasks with a glass-encased thermocouple wire (copper-constantan) pierced through the cap. The flask was placed in a styrofoam cup and surrounded by expanded polystyrene insulation.

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On the Mechanism of Formation of Azines from Hydrazones

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Introduction

During the past several years we have been involved in synthesis of mixed azines, $X_2C{=}N{-}N{=}CY_2$, where X and Y are moieties derived from ketones. $X_2C{=}O$ was typically naloxone (1) or naltrexone (2), i.e. opioid antagonists, and $Y_2C{=}O$ represented steroidal ketones.[1-5] These azines were typically prepared by a reaction of $X_2C{=}O$ (1 or 2) with the hydrazones of steroidal ketones, i.e. $Y_2C{=}N{-}NH_2$. The resulting azines, such as the mixed azines between estrone (3) and 1 or 2 (4, 5), showed a range of unexpected biological activities ranging from the ultra-long-lasting opioid antagonist activity[4] to specificity for the opioid δ receptor subtype.[5] In order to further study the receptor requirements for the long-lasting and δ-specific activity, we prepared a series of azines of 1 or 2 with various nonsteroidal ketones, which were chosen for their steric shape and electronic distribution. Hydrazones of such ketones were prepared first, with the objective to couple them with 1 or 2.

In the course of synthesis of these hydrazones by treatment of the corresponding ketones with an excess of hydrazine hydrate, with or without acid catalyst, we made the following observations. Some ketones gave virtually quantitative yields of hydrazones. Some other ketones, on the other hand, gave very low yields of hydrazones but high yield of azines. Some sterically hindered ketones gave hydrazones in low yields with a great difficulty; yet the hydrazones, once formed, were easily converted into the azines upon standing.

The objective of this paper is to present these various ketone categories and to suggest some possible factors which influence the formation of hydrazones and azines. The ketone models, although chosen with the biological objectives in mind, do emcompass several important ketone categories, such as cyclic, sterically hindered, conjugated, etc.

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