Addition–Displacement Reactions of Electron-Deficient Aromatics. Formation of Indole, Benzoquinoline, and Quinoline or Isoquinoline Derivatives

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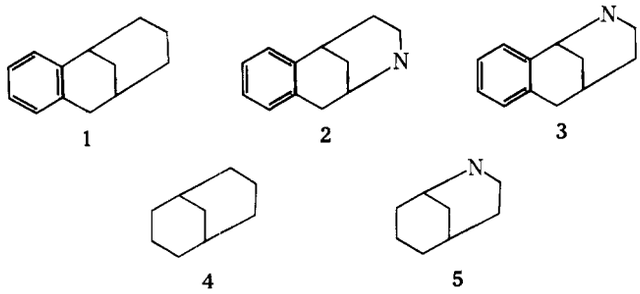
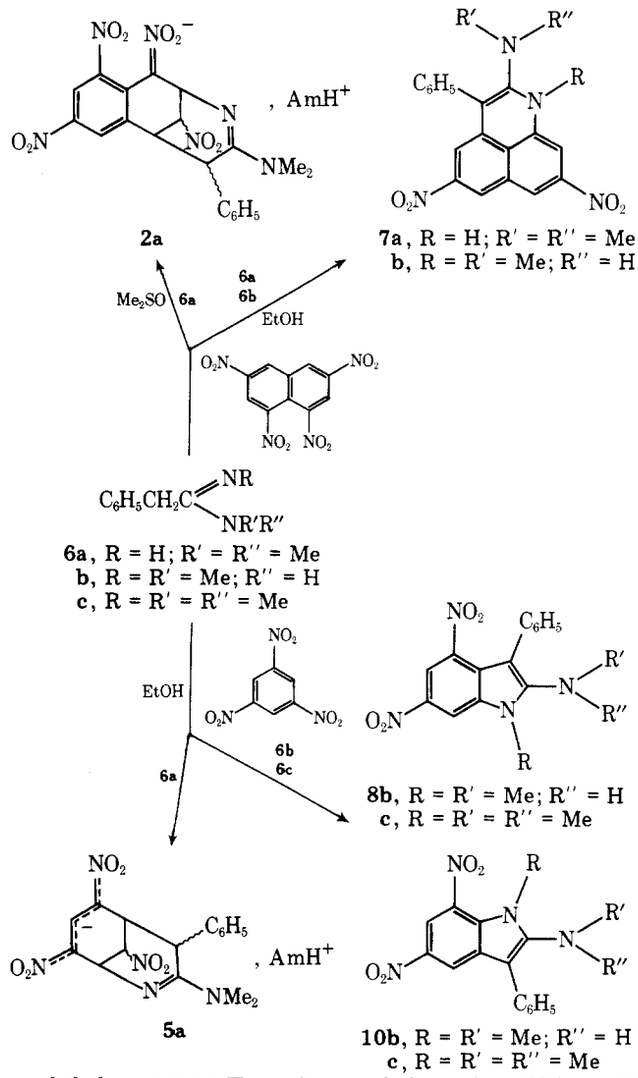
Reactions of amidines with electron-deficient benzenes and naphthalenes are shown to yield heteroaromatic compounds. These reactions are in contrast to those yielding meta-bridged products which can form from similar substrates. N-Methylated α-phenylacetamidines were reacted with *sym*-trinitrobenzene to give substituted indoles, with 1,3,6,8-tetranitronaphthalene to give benzoquinoline derivatives, and with 3,5-dinitrobenzophenone to produce a substituted quinoline or isoquinoline derivative.

We have previously reported the formation of highly functionalized derivatives of the bicyclic ring systems **1–5**,



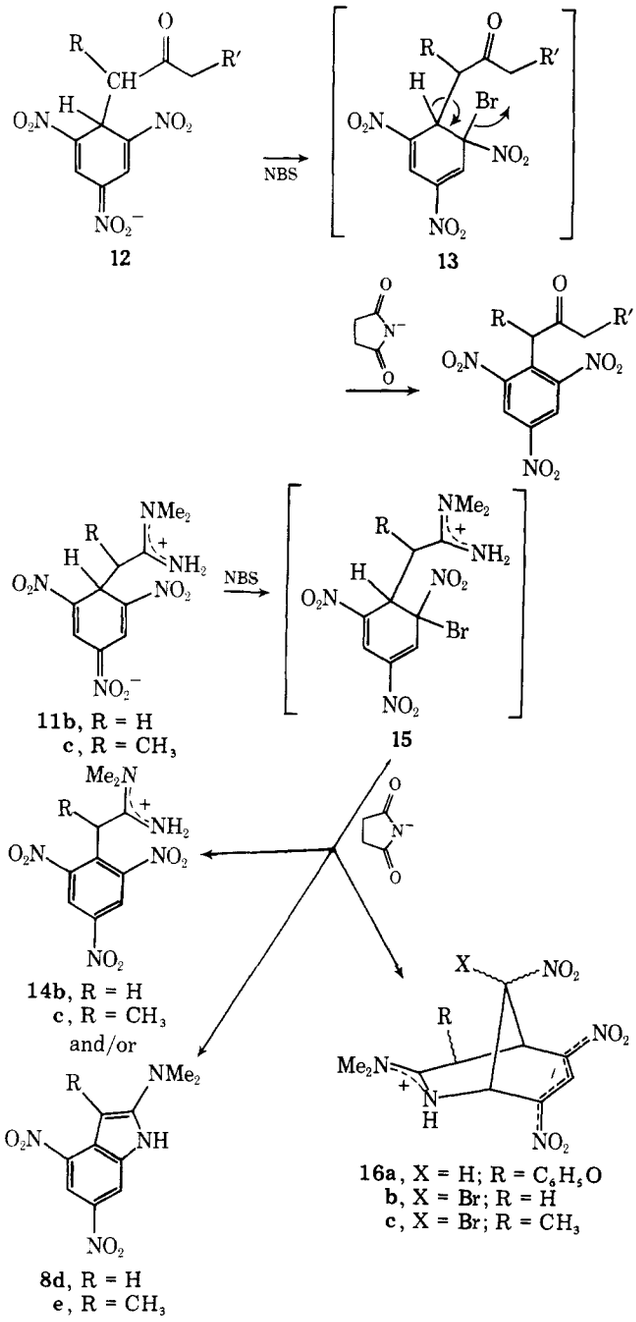
which result from meta bridging of nitronaphthalenes and nitrobenzenes with carbanions and amidines.[1–6] We and others have also reported the observation that a carbonyl-containing substituent in the electron-deficient benzene substrate results in either meta-bridged bicyclics (**4**) or naphthalenes depending on the nature of the attacking nucleophile.[7,8] We now report other modes of cyclization involving intramolecular nitrite displacement or intramolecular nucleophilic addition which lead to indole, isoquinoline or quinoline, and benzoquinoline derivatives. We also report a new oxidative mechanism for meta bridging. These reactions extend the utility of synthetic methods involving neighboring group interaction in ortho-substituted nitrobenzenes, an area recently reviewed by Preston and Tennant.[9]

The reactions of amidines with nitronaphthalenes and nitrobenzenes leading to bridged adducts containing the ring systems **2, 3,** and **5** were in most cases carried out in Me_2SO.[2,3,5,6] In several instances however, changing the solvent to ethanol results in an entirely different product. For example, reaction of α-phenyl-*N,N*-dimethylacetamidine (**6a**) with 1,3,6,8-tetranitronaphthalene in Me_2SO affords the red-orange bicyclic adduct **2a**.[2,6] The same reaction in ethanol yields purple crystals of a different product which analyzes correctly for a 1:1 adduct of amidine and aromatic minus $H_2N_2O_4$. A parent peak in the mass spectrum at *m/e* 376 supports the loss of two nitro groups, and the ^1H NMR spectrum and elemental analyses (see Experimental Section) substantiate the structure as benzoquinoline **7a**. Preparation of **7a** from C-1 deuterated 1,3,6,8-tetranitronaphthalene provides a product with diminished ^1H NMR intensities for the two aromatic peri protons at δ 8.22 and 9.40. Double nitrite displacement is not entirely unexpected. The peri nitro groups in 1,3,6,8-tetranitronaphthalene are in very close proximity and the resulting nonbonded repulsions would be expected to distort the planarity of the π system.[10] One other double displacement of two peri nitro groups has been reported.[11] Both nitro groups in 1,8-dinitronaphthalene are displaced photochemically in chloroform–HCl to afford 1,8-dichloronaphthalene. 1,3,6,8-Tetranitronapthalene after 100 h at pH 10.6 reacts to yield more than 1 equiv of nitrite ion.[12a]



Reaction of 1,3,6,8-tetranitronaphthalene with α-phenyl-*N,N'*-dimethylacetamidine (**6b**) yields the *N,N'*-dimethyl analogue **7b**. The structure is again confirmed by the elemental analyses, ^1H NMR, and mass spectra, further substantiating the loss of both peri nitro groups (see Experimental Section).

We have previously found that α-phenyl-*N,N*-dimethylacetamidine (**6a**) reacts with *sym*-trinitrobenzene (TNB) to give the bridged adduct **5a**, analogous to the bridged adduct **2a**, formed from 1,3,6,8-tetranitronaphthalene and **6a** in Me_2SO.[2,6] Surprisingly, **5a** is formed from **6a** and TNB even



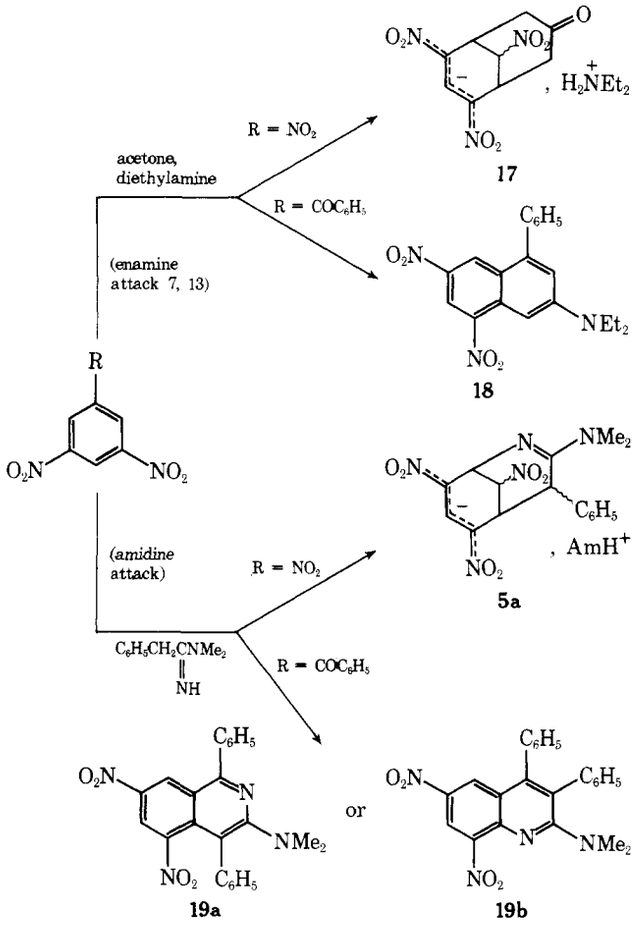
in ethanol, whereas **7a** is the only isolable product in this protic solvent with the naphthalene substrate. In order to more fully characterize the spectrum of amidine reactivity with TNB, the *N,N'*-dimethyl- and *N,N,N'*-trimethyl-α-phenylacetamidines **6b** and **6c** were reacted with this aromatic in ethanol. A dramatic difference in reactivity between these amidines and the *N,N*-dimethyl derivative **6a** was observed. With **6b**, red crystals of a product analyzing correctly for $C_{16}H_{14}N_4O_4$ were obtained. In chloroform this product shows strong maxima at 335 and 449 nm. The ^1H NMR spectrum shows two doublets (J = 3 Hz) at δ 8.36 and 8.75, which are consistent with an unsymmetrical 1,2,3,5-substituted benzene. The loss of a nitro group, indicated by the elemental analyses, and the previous observations of addition[2,6] and nitrite displacement reactions involving amidines and nitroaromatics (vide supra) provide substantial evidence for indole **8b** or **10b**. A five-proton multiplet for the phenyl at δ 7.37, a three-proton singlet at δ 3.86 for the indole *N*-methyl, and a three-proton doublet at δ 2.92 for the exocyclic *N*-methyl comprise the rest of the spectrum (the NH absorption overlaps the aromatic multiplet).

With the trimethylamidine **6c** an analogous compound is formed (**8c** or **10c**). The complete ^1H NMR spectrum, as well as pertinent UV, IR, mass spectral, and electronic absorptions, are summarized in the Experimental Section.

Interestingly, when the filtrate from the reaction of **6c** and TNB is reduced in volume and chromatographed, the material obtained shows a ^1H NMR spectrum consistent with two isomers in a ratio of 4:1. The resonances of the major isomer are identical with those of the isolated crystalline product. Those of the minor isomer are similar to those of the product isolated from the reaction of **6b** and TNB. The minor product could not be isolated in pure form.

In an attempt to form products analogous to **8** via a different route, the well-characterized zwitterionic amidinium σ complexes **11b** and **11c**[2] were reacted with *N*-bromosuccinimide. Ketonic σ complexes like **12** undergo oxidation to the corresponding picryl ketone with this reagent,[12b] presumably via formation of **13**, followed by elimination of HBr. The reaction with **11** did not follow this course, however. Instead of products like **8** or **14**, a dark red, crystalline material was isolated which was shown to contain bromine. For example, reaction of **11b** with NBS yields a compound which analyzes correctly for $C_{10}H_{12}N_5O_6Br$. The visible and ^1H NMR spectra of this material are consistent with **16b**. Comparisons with ^1H NMR and visible spectra of **16a**, prepared by a different method,[6] provide definitive evidence for structure **16b**. The reaction of **11c** with NBS yields the analogous bridged ion **16c**. It is possible that elimination of HBr from **15** occurs less rapidly than intramolecular cyclization to **16**. The different behavior of the presumed intermediates **13** and **15** may also be related to the acidity of the C–H and N–H protons in the exocyclic side chains. Proton abstraction from carbon (in **13**) and nitrogen (in **15**) must precede cyclization.[3]

The reactivity of α-phenyl-*N,N*-dimethylacetamidine (**6a**) and enamines toward symmetrically substituted di- and



trinitrobenzenes shows interesting similarities. We have previously shown that the enamine of acetone and diethylamine forms a meta-bridged product **17** with *sym*-trinitrobenzene,[13] but forms the ortho substituent cyclized product, naphthalene **18**, with 3,5-dinitrobenzophenone.[7] Also, the bridged adduct **5a** results from reaction of **6a** with *sym*-TNB.[2,6] We now show that reaction of 3,5-dinitrobenzophenone with this amidine yields a highly functionalized nitroquinoline or nitroisoquinoline.

Reaction of 3,5-dinitrobenzophenone and α-phenyl-*N,N*-dimethylacetamidine (**6a**) yields red crystals of a compound with visible maxima similar to those of **18** (see Experimental Section). The ^{1}H NMR spectrum of this product is similar to that of **18** with two coupled doublets for the nitroaromatic ring protons at δ 8.62 and 9.06 (1 H each), two five-proton multiplets at δ 7.48 and 7.53 for the two phenyl groups, and a six-proton singlet at δ 2.90 for the *N*-methyls. The elemental analyses further substantiate structure **19.** An unequivocal distinction between **19a** and **19b** cannot be made.

Experimental Section

All melting points are uncorrected. ^{1}H NMR spectra were run on JEOL C-60-HL and MH-100 spectrometers with Me_4Si as an internal reference. Visible and ultraviolet spectra were recorded on a Perkin-Elmer Model 402 UV–visible spectrophotometer. Infrared spectra were recorded on a Perkin-Elmer Model 237B infrared spectrophotometer. Mass spectra were obtained on a Perkin-Elmer RMU-6D mass spectrometer. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn., and G. I. Robertson Laboratories, Florham Park, N.J.

Amidines. α-Phenyl-*N,N*-dimethylacetamidine was prepared as reported previously.[2] α-Phenyl-*N,N'*-dimethylacetamidine was prepared by two methods.

Method A. A solution of 14.9 g of α-phenyl-*N*-methylacetamide in 150 ml of methylene chloride was added to 100 ml of a 1 M methylene chloride solution of triethyloxonium tetrafluoroborate and the mixture was stirred for 24 h. After reduction to ⅓ the original volume 22 ml of 5.45 M methylamine in ethanol was added and the resulting mixture was stirred for 72 h. The solvent was then removed under vacuum to give an oil which was added to 8 M NaOH, followed by extraction with chloroform. The extracts were dried over Na_2SO_4 and the chloroform removed by distillation. Fractional distillation of the residue yielded 10.2 g of amidine, bp 94 °C (0.13 mm). The ^{1}H NMR spectrum ($CDCl_3$) showed singlets at δ 2.76 (6 H, NMe), 3.44 (2 H, CH_2), 4.12 (1 H, NH, br), and a multiplet at δ 7.02 (5 H, C_6H_5). The IR spectrum showed strong bands at 3250 and 1615 cm^{-1}.

Method B. With vigorous stirring, 32 g of ethyl α-phenylacetimidate hydrochloride was added to a solution of 21.1% methylamine in 100 ml of ethanol. After 3 days the solution volume was reduced under vacuum and the residue was added to an additional 100 ml of 21.1% methylamine solution and stirred for 3 more days. The solvent was then removed under vacuum and the residue was stirred with anhydrous ether. The resulting solid was recrystallized from ethanol to give a white, crystalline product with mp 208–210 °C (lit.[14] 210 °C). The free base was obtained by treating the hydrochloride salt with an equimolar amount of sodium ethoxide in ethanol, filtering off the sodium chloride, and fractionally distilling the filtrate.

α-Phenyl-*N,N,N'*-trimethylacetamidine was prepared by adding 50 ml of 1 M triethyloxonium tetrafluoroborate in methylene chloride to a rapidly stirred solution of 7.45 g of α-phenyl-*N*-methylacetamide in 75 ml of the same solvent. The mixture was stirred for 24 h and the volume was then reduced to 40 ml. The remaining solution was then mixed with 11 ml of 5.21 M dimethylamine in anhydrous ethanol and stirred for 3 days. Removal of the solvent afforded a viscous oil which was treated with 8 M NaOH and extracted with chloroform. The extracts were dried over sodium sulfate and the chloroform was removed by distillation. The residue was fractionally distilled to afford 6.3 g of product, bp 61–63 °C (0.025 mmHg). The ^{1}H NMR spectrum ($CDCl_3$) showed singlets at δ 2.86 (6 H, NMe_2), 3.06 (3 H, C=NMe), 3.81 (2 H, CH_2), and a multiplet at δ 7.31 (5 H, C_6H_5). The IR showed a strong band at 1625 cm^{-1}.

Preparation of 7a. Mixing 30 ml of ethanol containing 0.49 g of α-phenyl-*N,N*-dimethylacetamidine with 350 ml of ethanol containing 0.31 g of 1,3,6,8-tetranitronaphthalene resulted in a dark purple solution. After standing for 21 days at room temperature the resulting purple crystals were filtered, washed with ethanol and ether, and dried at 60 °C (1 mmHg) for 12 h. The resulting product (0.16 g, 41%) had mp 297–299 °C and analyzed correctly for $C_{20}H_{16}N_4O_4$: C, 63.83; H, 4.29; N, 14.89. Found: C, 63.90; H, 4.51; N, 14.79. In Me_2SO **7a** shows absorption maxima at 411 and 585 nm. Strong IR absorption bands (KBr) occur at 3340, 1635, 1585, 1550, and 1525 cm^{-1}. A parent peak at *m/e* 376 appears in the mass spectrum, along with M + 1 and M + 2 peaks at 377, 378, and peaks at 346 (−NO), 330 ($-NO_2$), 284 ($-2NO_2$), 213, and 193. The ^{1}H NMR spectrum (Me_2SO-d_6) shows absorptions at δ 3.07 (6 H, s), 7.62 (5 H, m), 8.21 (1 H, s, br), 8.27 (1 H, s, br), 8.87 (1 H, d, J = 3 Hz), 9.42 (1 H, d, J = 3 Hz), 11.77 (1 H, br).

Preparation of 7b. This compound was obtained in 72% yield from reaction of 1,3,6,8-tetranitronaphthalene and α-phenyl-*N,N'*-dimethylacetamidine in the same fashion as **7a.** The crystalline product obtained in 71% yield had mp 276–278 °C and analyzed correctly for $C_{20}H_{16}N_4O_4$: C, 63.83; H, 4.29; N, 14.89. Found: C, 63.89; H, 4.34; N, 14.84. In Me_2SO **7b** shows visible absorption maxima at 407 and 659 nm. Strong IR bands (KBr) occur at 3420, 1630, 1565, 1530 cm^{-1}. A parent peak appears at *m/e* 376 in the mass spectrum. The ^{1}H NMR spectrum (Me_2SO-d_6) shows absorptions at δ 2.76 (3 H, d, J = 3 Hz), 3.70 (3 H, s), 7.28 (1 H, br), 7.65 (5 H, m), 8.22 (1 H, br), 8.31 (1 H, br), 8.88 (1 H, d, J = 2 Hz), and 9.30 (1 H, d, J = 2 Hz).

Reaction of TNB and 6c. A mixture of 0.83 g of α-phenyl-*N,N,N'*-trimethylacetamidine and 0.69 g of *sym*-trinitrobenzene in 50 ml of absolute ethanol was allowed to stand at room temperature for 3 days. The resulting orange solid was filtered off and recrystallized from chloroform–methanol to afford a crystalline solid which after drying at 70 °C (0.1 mmHg) for 4 h yielded 0.19 g of crystalline product which melted at 226–227 °C. An additional 0.3 g of powdery product was obtained by evaporating the solvent from the filtrate and chromatographing the residue on a silica gel column with chloroform. The crystalline material analyzed correctly for $C_{17}H_{16}N_4O_4$: C, 60.00; H, 4.74; N, 16.46. Found: C, 60.01; H, 4.69; N, 16.72. In chloroform it shows visible maxima at 346 and 428 nm. Strong IR bands (KBr) occur at 2935, 2850, 2935, 1605, 1540, 1520, and 1495 cm^{-1}. A parent peak appears at *m/e* 340 in the mass spectrum along with M + 1 and M + 2 peaks at *m/e* 341 and 342, and peaks at *m/e* 310 (−NO), 295 ($-NHMe_2$), 278, 263, 248, 233, and 218. The ^{1}H NMR spectrum ($CDCl_3$) shows absorptions at δ 2.66 (6 H, s), 3.76 (3 H, s), 7.18 (2 H, m), 7.31 (3 H, m), 8.33 (1 H, d, J = 2 Hz), and 8.48 (1 H, d, J = 2 Hz).

Reaction of TNB and 6b. This reaction was carried out in a fashion similar to the reaction of TNB and **6c** using 0.74 g of aromatic and 1.12 g of **6b.** After removal of solvent from the reaction mixture the residual oil was purified by column chromatography (silica gel–chloroform) to yield a solid which was recrystallized from methanol–chloroform to yield red crystals. These were washed with cold methanol and dried at 80 °C (0.1 mmHg) for 4 h to yield 0.21 g of product, mp 191 °C, which analyzed correctly for $C_{16}H_{14}N_4O_4$: C, 58.89; H, 4.32; N, 17.17. Found: C, 59.10; H, 4.36; N, 16.99. In chloroform **10** shows visible maxima at 335 and 449 nm. The ^{1}H NMR spectrum ($CDCl_3$) shows absorptions at δ 2.92 (3 H, d, J = 6 Hz), 3.86 (3 H, s), 4.36 (1 H, bd), 7.37 (5 H, m), 8.36 (1 H, d, J = 3 Hz), and 8.75 (1 H, d, J = 3 Hz).

Preparation of 16b. A solution of 0.19 g of NBS in 30 ml of ethanol was added dropwise, over a period of 2 h, to a rapidly stirred solution of 0.33 g of the σ complex **11b** in 100 ml of ethanol. After stirring for an additional 4 h the resulting red, crystalline material was filtered, washed with additional ethanol and ether, and then vacuum dried at 60 °C to give 0.18 g of **16b,** mp 222–224 °C. In Me_2SO **16b** shows maxima at 300 and 491 nm. It analyzes correctly for $C_{10}H_{12}N_5O_6Br$: C, 31.76; H, 3.20; N, 18.52. Found: C, 31.50; H, 3.33; N, 18.30. The ^{1}H NMR spectrum (Me_2SO-d_6) shows absorptions at δ 3.05 (3 H, s), 3.10 (3 H, s), 3.31 (2 H, m), 4.51 (1 H, m), 5.59 (1 H, d), 8.50 (1 H, s), and 10.22 (1 H, br). IR absorptions (KBr) occur at 3400–2200, 1640, 1565, 1530, 1385, and 1335 cm^{-1}.

Preparation of 16c. This compound was prepared in a fashion similar to that used for **16b,** at 0 °C. The crystalline product obtained in 50% yield had mp 172–173 ° and analyzed correctly for $C_{11}H_{14}N_5O_6Br$: C, 33.69; H, 3.60; N, 17.86. Found: C, 33.80; H, 3.87; N, 17.97. The ^{1}H NMR spectrum (Me_2SO-d_6) showed absorptions at δ 1.22 (3 H, d), 3.13 (6 H, s), 3.67 (1 H, m), 4.42 (1 H, br s), 5.94 (1 H, br s), 8.42 (1 H, s), and 10.16 (1 H, br), In Me_2SO **16c** shows maxima at 300 and 493 nm.

Preparation of 19. This compound was prepared by mixing 1.46 g of 3,5-dinitrobenzophenone with 1.71 g (mmol) of α-phenyl-*N,N*-dimethylacetamidine and heating the mixture to 60 °C with stirring. After 20 min the mixture was cooled and allowed to stand at room temperature for 48 h. Addition of 10 ml of ethanol and filtration of

the resulting solution resulted in a red powder, which was recrystallized from chloroform–methanol. The resulting red crystals (1.5 g, 68%) had mp 243–245 °C and analyzed correctly for $C_{23}H_{18}N_4O_4$: C, 66.66; H, 4.38; N, 13.52. Found: C, 66.80; H, 4.40; N, 13.27. The mass spectrum had a parent peak at *m/e* 414, M + 1 and M + 2 peaks at *m/e* 415 and 416, and peaks at *m/e* 413, 398, 397, 385, 384, 370, 368, 350, 339, 337, and 323. The IR spectrum (KBr) showed strong bands at 2920, 1600, 1575, 1565, 1530, 1385, 1335, and 1315 cm^{-1}. Strong visible maxima appeared at 476, 426, and 280 nm in Me_2SO, 478, 420, and 250 nm in chloroform, and 456, 412, and 247 nm in methanol. The ^1H NMR spectrum (Me_2SO-d_6) showed absorptions at δ 2.90 (6 H, s), 7.53 (5 H, m), 7.78 (5 H, m), 8.62 (1 H, d, J = 3 Hz), and 9.06 (1 H, d, J = 3 Hz). In $CDCl_3$ the spectrum showed absorptions at δ 2.95 (6 H, s), 7.66 (5 H, m), 7.96 (5 H, m), 8.76 (1 H, d, J = 3 Hz), and 9.22 (1 H, d, J = 3 Hz).

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Registry No.—**6a,** 56776-16-0; **6b,** 52066-17-8; **6c,** 60719-04-2; **7a,** 60719-05-3; **7b,** 60719-06-4; **8b/10b,** 60719-26-8; **8c/10c,** 60719-27-9; **11b,** 56776-17-1; **11c,** 56776-18-2; **16b,** 60719-07-5; **16c,** 60719-08-6; **19a,** 60719-09-7; **19b,** 60719-10-0; α-phenyl-*N*-methylacetamide, 6830-82-6; methylamine, 74-89-5; ethyl α-phenylacetimidate hydrochloride, 5442-34-2; dimethylamine, 124-40-3; 1,3,6,8-tetranitronaphthalene, 28995-89-3; TNB, 99-35-4; NBS, 128-08-5; 3,5-dinitrobenzophenone, 51911-74-1.

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Structural Studies of Organosulfur Compounds. 2.[1] Conformational Analysis of 2-Methoxy-*trans*-hexahydro-1,4-benzoxathianes

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The 2-methoxy substituent in the 1,4-oxathiane prefers the *equatorial* conformation where the $\Delta G°$'s range from −0.23 to −0.49 kcal/mol (axial ⇄ equatorial), in a number of solvents as determined by direct acid catalyzed equilibration of the diastereoisomeric 2-methoxy-*trans*-hexahydro-1,4-benzoxathianes.

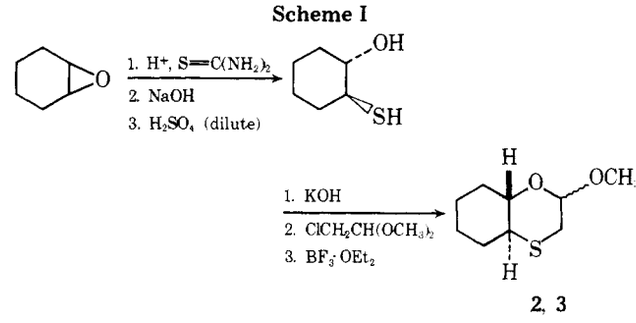
Recent reports indicate that the 2-methoxyl group in 1,4-oxathiane (**1**) may be slightly axial (56%)[2] or predominantly equatorial (75%)[3] in acetonitrile where presumably the anomeric effect,[4] van der Waals steric interactions, and the recently coined "hockey sticks" effect[2] collectively control its conformational preference. The conflicting results of these investigations[2,3] and other recent studies involving conformational predictions in some nucleoside derivatives of 1,4-oxathiane[5] have suggested the need for quantitative determinations of conformational energies of C-2 and possibly C-3 substituents in the 1,4-oxathiane system.

While conformational preferences of substituents derived from time-averaged intensive parameters (e.g., coupling constants and chemical shifts) of conformationally mobile systems and model systems are greatly influenced by the limitations of the models, direct chemical equilibrations of the appropriate model diastereoisomers (if practical) and direct observation of the conformers of conformationally mobile systems by NMR techniques are generally preferred[6] (Figure 1). However, solvent-dependent investigations are hampered by the inaccessibility of suitable solvents for low-temperature NMR determinations. In this report, we chose to put the conformational preference of the 2-methoxyl group in the 1,4-oxathiane system on a firm basis by determining its conformational free energy in a number of solvents by direct chemical equilibration of model diastereoisomers.

Results and Discussion

The diastereoisomers of 2-methoxy-*trans*-hexahydro-1,4-benzoxathiane (**2** and **3**) were envisioned as ideal models for the two chair conformations of 2-methoxy-1,4-oxathiane (**1**) since they would ensure conformational rigidity of the 1,4-oxathiane ring and allow for minimum distortions in the ring system. The compounds, **2** and **3,** were prepared by reacting a basic solution of *trans*-2-mercaptocyclohexanol, prepared from the addition of thiourea to cyclohexene oxide, with chloroacetaldehyde dimethyl acetal to afford the open chain acetal followed by condensation with boron trifluoride etherate (Scheme I). Separation of the stereoisomers was accomplished with spinning band column distillations, low-temperature crystallizations, and preparative gas chromatography (see Experimental Section).

Scheme I



2, 3

The stereochemistry of the C-2 methoxyl group in **2** and **3** was ascertained by ^1H NMR coupling constants and both proton and carbon chemical shifts. For example, the sample exhibiting the low-field "triplet" pattern for C-2 H at δ 4.75 ppm is suggestive of nearly equivalent vicinal couplings between the C-2 proton and the geminal C-3 protons. Application of the Karplus relationship to these couplings aided in