Facile Intramolecular Tosylhydrazone-Mediated Cyclopropanation Reactions of 4-(2-Formylphenyl)-1,4-dihydropyridines

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Hantzsch-type 4-(2-formylphenyl)-1,4-dihydropyridine derivatives **4–7** undergo facile intramolecular tosylhydrazone-mediated cyclopropanation reactions to afford the highly constrained analogues **16–19**, respectively. Prior formation of the conjugate anions of the tosylhydrazones **8–11** is not required for this conversion, whereas cyclopropane derivatives are normally formed by thermolysis of such salts. Rather, formation of cyclopropanes **16–19** probably involves iminium ion mediated nucleophilic attack of C(3) on the arylformimino carbon atom, followed by pyrazoline ring formation via intramolecular attack of nitrogen on the electrophilic C(2) carbon atom (**26** → **27**). Structural assignments of the intermediate pyrazolines and product cyclopropanes are based on ^{1}H NMR spectroscopy and X-ray crystallographic analysis.

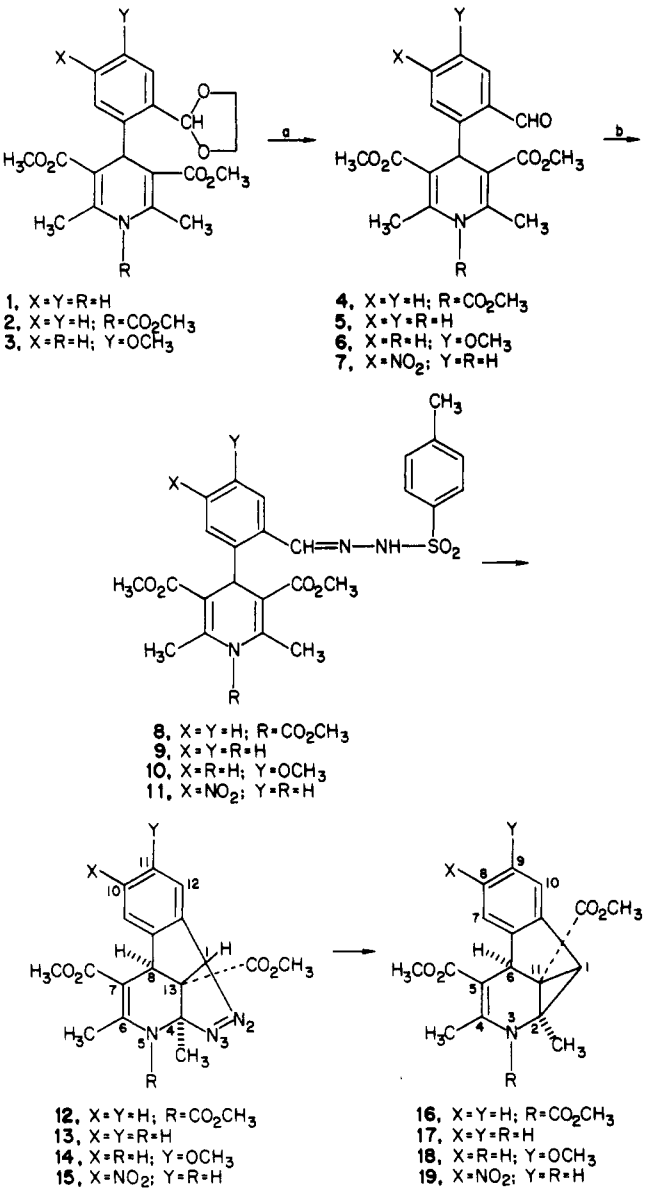
Although Hantzsch first enunciated his dihydropyridine synthesis over 100 years ago,[1a-c] only in the past two decades have 4-aryl-1,4-dihydropyridine derivatives been recognized as a rich source of pharmacologically active compounds.[2a,b] Indeed, one of these compounds, nifedipine,[3] was recently introduced as a new and clinically important calcium channel blocking agent for use in the treatment of certain cardiovascular disorders. Although little is known concerning the preferred or requisite conformation of these dihydropyridines at the pharmacologically active site or receptor,[4,5] recent studies have been directed toward the synthesis of conformationally restricted 4-aryl-1,4-dihydropyridine analogues in order to study such geometrical requirements.[6-10] In the present paper, we now report the synthesis of a group of highly constrained derivatives obtained by facile intramolecular tosylhydrazone-mediated cyclopropanation reactions of 4-(2-formylphenyl)-1,4-dihydropyridines.

Results

At the outset of this research, we intended to prepare tosylhydrazone derivatives of 4-(2-formylphenyl)-1,4-dihydropyridines and to study the products arising from thermal decomposition of their lithium or sodium salts.[11] Diazo compounds, resulting from thermolysis of such salts,[12] are known to undergo a variety of intramolecular addition reactions to adjacent olefinic linkages, via carbene or 1,3-dipolar cycloaddition reactions, and to afford cyclopropane derivatives either directly or by thermal fragmentation of pyrazoline intermediates.[13-15]

Acylation of dimethyl 2,6-dimethyl-4-(2-[2-(1,3-dioxolanyl)]phenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**1**)[9] with sodium hydride and methyl chloroformate, followed by acetal deprotection of **2** with *p*-toluenesulfonic acid in acetone, afforded **4** in 22% overall yield (Scheme I). The crystalline, stable tosylhydrazone **8** then was prepared by allowing equivalent quantities of **4** and tosylhydrazine to react in benzene at room temperature for 1.5 h. Surprisingly, cyclopropane **16** was obtained directly from this hydrazone derivative on refluxing in benzene for 2 h. The structure of **16**, originally assigned on the basis of its 360-MHz ^{1}H NMR spectrum, elemental analysis, and mass spectrum, was subsequently confirmed by single-crystal X-ray analysis (Figure 1).

Scheme I[a]



[a] (a) TsOH, acetone; (b) $H_2NNHSO_2C_6H_4CH_3$; (c) heat.

Since the facile thermolytic formation of **16** and **8** did not require prior salt formation using strong base,[16] a

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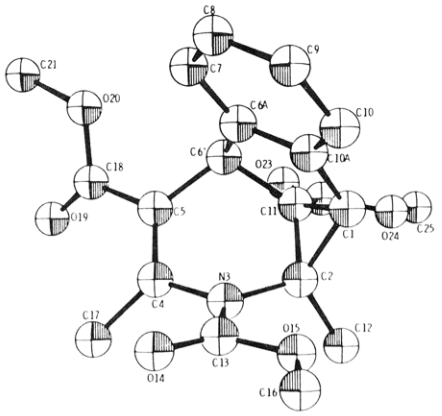


Figure 1. Computer-generated drawing of **16** derived from the X-ray coordinates with hydrogens omitted for clarity.

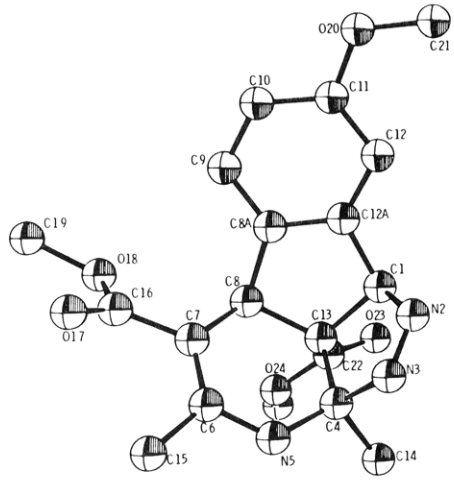
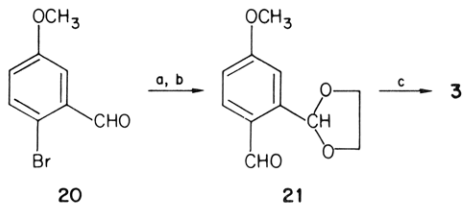


Figure 2. Computer-generated drawing of **14** derived from X-ray coordinates with hydrogens omitted for clarity.

similar reaction sequence was carried out on the unprotected dihydropyridine **5**.[9] Reaction of **5** with 1 equiv of tosylhydrazine in benzene at room temperature for 1 h gave a crystalline precipitate that proved to be the labile tosylhydrazone **9**. On continued stirring of the reaction mixture, all of this precipitate redissolved within 2 h; evaporation of the benzene afforded only pyrazoline **13**. The structure of **13**, originally assigned on the basis of its 360-MHz ^{1}H NMR spectrum, was subsequently confirmed by comparison of this spectrum with that of **14**, the structure of which was established by single-crystal X-ray analysis (Figure 2). Refluxing a solution of **13** in benzene, or merely melting it, converted this intermediate to cyclopropane **17**. The structural assignment for **17** rests on comparative spectroscopic evidence with that of the established cyclopropane **16**. Although **9** and **13** were rather labile, both could be isolated in essentially pure form as described above. Attempted purification of either by conventional crystallization procedures, however, led to mixtures of **13** and **17**. Tosylhydrazone **9** displayed an interesting solvent-dependent NMR behavior. In Me_2SO, **9** appeared to be stable indefinitely. Addition of $CDCl_3$ or DCl to the solution, however, resulted in the complete conversion of **9** to **13** over a period of several hours.

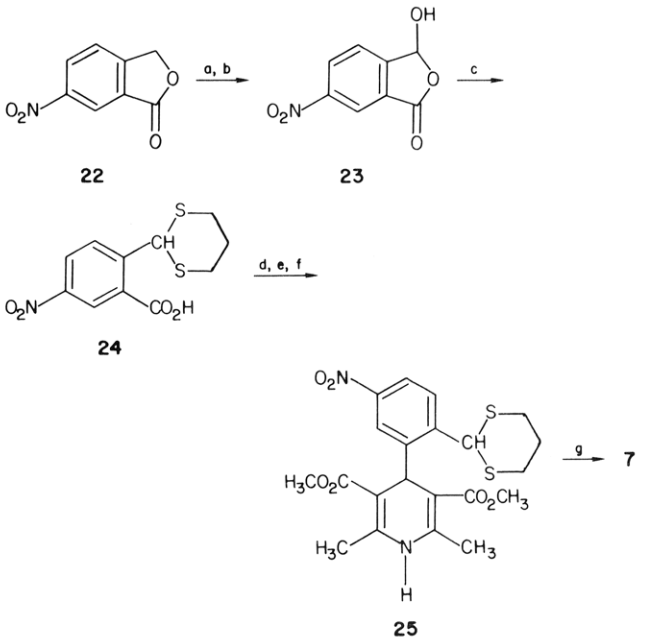
Attempted basic hydrolysis of the urethane moiety of **16** to give **17** led only to saponification of the nonconjugated ester group at C(11). However, the urethane moiety of **12** was selectively hydrolyzed at room temperature in methanolic potassium hydroxide, and heating the product of this reaction in benzene provided **17**.

Scheme II[a]



[a] (a) $HOCH_2CH_2OH$, TsOH; (b) (1) *n*-BuLi, (2) *N*-formylpiperidine; (c) $CH_3COCH_2CO_2CH_3$, $CH_3C(NH_2)=CHCO_2CH_3$.

Scheme III[a]



[a] (a) *N*-Bromosuccinimide, hν; (b) H_2O; (c) $(CH_2)_3(SH)_2$, $BF_3\cdot(C_2H_5)_2O$; (d) $BH_3\cdot THF$; (e) pyridinium chlorochromate; (f) $CH_3COCH_2CO_2CH_3$, $CH_3C(NH_2)=CHCO_2CH_3$; (g) HgO, $BF_3\cdot(C_2H_5)_2O$, THF, H_2O.

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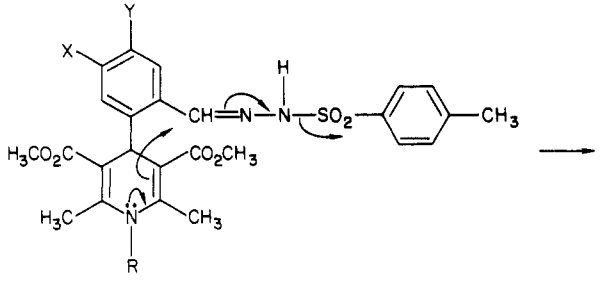
Recognizing that the nature and number of nuclear substituents, as well as their substitution pattern, greatly influences the pharmacological profiles of 4-aryl-1,4-dihydropyridines,[17-19] the tosylhydrazone-mediated cyclopropanation reaction was extended to two nuclear substituted analogues. The methoxy-substituted compound **3** was prepared from aldehyde **21** via the Hantzsch condensation (Scheme II), and the acetal was deprotected to give **6**. Reaction of **6** with tosylhydrazine at room temperature in benzene gave a 46% yield of **14** after chromatographic purification. The structure of **14**, as noted previously, was established by single-crystal X-ray analysis (Figure 2), and as was the case for **13**, **14** was smoothly converted to **18** in refluxing benzene (47% isolated pure yield) or by melting it. In a similar fashion, the *p*-nitrobenzaldehyde derivative **7**, formed as shown in Scheme III, was allowed to react with tosylhydrazine to afford **19** in 26% overall yield.

Discussion

Recent evidence now supports the contention that C(3) carbon atoms of 4-aryl-1,4-dihydropyridines possess nucleophilic character and, further, that such incipient nucleophiles can participate in intramolecular reactions.[20,21] Thus, the mechanism for formation of cyclopropane derivatives **16** to **19** most probably involves an iminium ion mediated intramolecular nucleophilic attack of C(3) on the arylformimino carbon atom (**26**) followed by pyrazoline ring formation via intramolecular attack of nitrogen on the electrophilic C(2) carbon atom (**27**). Intermediate **27** must



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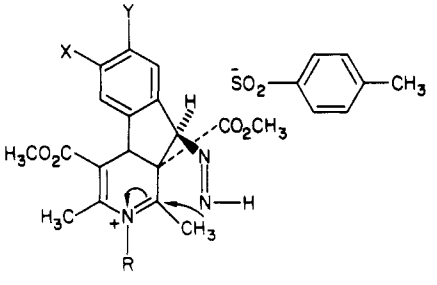

27

have the configuration shown for pyrazoline ring formation to occur. The epimer of **27**, in which the diazene moiety is in a geometrically unfavorable position, cannot undergo this subsequent ring formation. Thermal fragmentation of the intermediate pyrazolines, a process long recognized as a synthetic pathway to cyclopropane derivatives,[22] then affords the final products. In the case of urethane **4**, the electron lone pair on nitrogen is sufficiently delocalized as to allow isolation and characterization of the stable tosylhydrazone intermediate **8**. Delocalization of this lone pair is not sufficiently attenuated, however, as to preclude its participation at elevated temperatures.

The use of tosylhydrazones as substrates in the generation of aliphatic diazo compounds, for 1,3-dipolar cycloaddition or carbene reactions, is well documented. Notably, in all of these reactions and related Bamford–Stevens reactions,[23,24] the conjugate anion of the tosylhydrazone is required for reaction. There is no such absolute requirement, however, for the tosylhydrazones **8**–**11**. We, therefore, conclude that the tosylhydrazone-mediated cyclopropanation reaction described in this paper proceeds via an intramolecular reaction pathway that is mechanistically distinct from the normal cyclopropanation reaction which involves, as a first step, thermolysis of the anions of tosylhydrazone derivatives. A consideration of the pharmacological properties of these cyclopropane analogues with respect to their conformational rigidity and the geometrical requirements of the receptor site will be published elsewhere.

Experimental Section

Melting points were taken on a Thomas-Hoover Unimelt capillary melting point apparatus and are uncorrected. IR spectra were recorded on Perkin-Elmer Models 21 and 1420 spectrophotometers. A Varian EM390 or Nicolet NT360 spectrometer was used to record ^{1}H NMR spectra in deuterochloroform unless indicated otherwise. Proton chemical shifts are expressed in parts per million downfield from internal tetramethylsilane. X-ray diffraction data were recorded with an Enraf-Nonius automatic diffractometer. Analytical TLC was carried out on 250-μm, 5 × 20 cm, silica gel GF plates (Analtech, Inc., UV and I_2 visualization). Elemental analyses were performed by the analytical department of Merck Sharp & Dohme Research Laboratories, West Point, PA 19486.

Trimethyl 2,6-Dimethyl-4-(2-[2-(1,3-dioxolanyl)]-phenyl)-1,4-dihydropyridine-1,3,5-tricarboxylate (2). To a stirred suspension of sodium hydride (0.393 g of 61% NaH in mineral oil) in THF (80 mL) was added dropwise a solution of **1**[9] (3.73 g, 0.01 mol) in a mixture of 35 mL of THF and 8 mL of DMF. After the addition was complete, the mixture was refluxed for 15 min and then was cooled. Methyl chloroformate (0.945 g, 0.01 mol) was added, and the mixture was refluxed for 18 h. The reaction mixture was concentrated under vacuum, and the residue was taken up in ethyl acetate. A small amount of starting material was removed by filtration. The filtrate was washed with H_2O and brine, dried ($MgSO_4$), and concentrated to dryness. The resulting product was purified by chromatography (silica gel, eluting with 30% ethyl acetate in hexane) to afford 1.94 g (45%) of **2**. An analytical sample was prepared by recrystallization from ethyl acetate–hexane; mp 120.5 °C; ^{1}H NMR δ 2.47 (s, 6 H, CH_3), 3.68 (s, 6 H, OCH_3), 3.90 (s, 3 H, NCO_2CH_3), 4.03–4.24 (m, 4 H, OCH_2CH_2O), 5.47 (s, 1 H, C_4H), 6.26 (s, 1 H, OCHO), 6.97–7.6 (m, 4 H, Ar H). Anal. Calcd for $C_{22}H_{25}NO_8$: C, 61.24; H, 5.84; N, 3.25. Found: C, 61.02; H, 5.99; N, 3.36.

Trimethyl 2,6-Dimethyl-4-(2-[(2-[(4-methylphenyl)-sulfonyl]hydrazono)methyl]phenyl)-1,3,5(4*H*)-pyridinetricarboxylate (8). A solution of 1.15 g (0.00267 mol) of **2** in 100 mL of acetone containing a catalytic amount of *p*-toluenesulfonic acid monohydrate was stirred at room temperature for 2.5 h. The solution was concentrated under reduced pressure, and the residue was dissolved in methylene chloride. After being washed with a dilute solution of sodium bicarbonate and then brine, the solution was dried ($MgSO_4$), filtered, and concentrated.

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The residue was purified by flash chromatography on silica gel. Elution with 50% ethyl acetate–hexane afforded 0.50 g (49%) of oily aldehyde **4**, characterized by its ^{1}H NMR spectrum: ^{1}H NMR δ 2.54 (s, 6 H, CH_3), 3.68 (s, 6 H, OCH_3), 3.90 (s, 3 H, NCO_2CH_3), 5.89 (s, 1 H, C_4H), 7.1–7.9 (m, 4 H, Ar H), 10.69 (s, 1 H, CHO).

A solution of 1.70 g (0.0044 mol) of the above aldehyde (**4**) and 0.819 g (0.0044 mol) of recrystallized tosylhydrazine in 75 mL of benzene was stirred at room temperature for 1.5 h. The solvent was evaporated. The product was purified by flash chromatography (silica gel, 35% ethyl acetate in hexane) to afford 1.7 g (70%) of pure **8**: mp 125–126 °C; IR 3200 (NH), 1715 (CO) cm^{-1}; ^{1}H NMR 2.42 (s, 3 H, Ar CH_3), 2.46 (s, 6 H, CH_3), 3.59 (s, 6 H, OCH_3), 3.85 (s, 3 H, NCO_2CH_3), 5.28 (s, 1 H, C_4H), 6.9–8.3 (m, 8 H, Ar H), 8.5 (s, 1 H, CH=N). Anal. Calcd for $C_{27}H_{29}N_3O_8S$: C, 58.37; H, 5.26; N, 7.56. Found: C, 58.70; H, 5.53; N, 7.56.

Trimethyl 1,2,3,6α-Tetrahydro-2,4-dimethyl-1,2,6-metheno-3-benzazocine-3,5,11α-tricarboxylate (16). A solution of **8** (1.1 g, 0.0020 mol) in benzene (100 mL) was refluxed for 2 h. The solution was evaporated to dryness, and the residue was purified by flash chromatography (silica gel, 30% ethyl acetate in hexane) to afford 0.33 g (45%) of pure **16**: mp 99–100 °C; IR 1700–1750 (CO) cm^{-1}; ^{1}H NMR δ 1.68 (s, 3 H, C_2CH_3), 2.33 (s, 3 H, C_4CH_3), 3.19 (s, 1 H, C_1H), 3.38 (s, 3 H, OCH_3), 3.74 (s, 3 H, OCH_3), 3.90 (s, 3 H, OCH_3), 5.04 (s, 1 H, C_6H), 7.0–7.2 (m, 4 H, Ar H); Mass spectrum, m/e 371 (M^+). Anal. Calcd for $C_{20}H_{21}NO_6$: C, 64.68; H, 5.70; N, 3.77. Found: C, 64.92; H, 5.80; N, 3.42.

Reaction of Dimethyl 2,6-Dimethyl-4-(2-formylphenyl)-1,4-dihydropyridine-3,5-dicarboxylate (5) with Tosylhydrazine. A. Formation of Tosylhydrazone 9. A solution of 0.50 g (0.0015 mol) of **5** and 0.30 g (0.0016 mol) of tosylhydrazine in 50 mL of benzene was stirred at room temperature for 1 h. The precipitate that formed was removed by filtration to afford 0.55 g (70%) of **9**. The product was examined immediately: TLC, single spot, R_f 0.35 (1:1 ethyl acetate–hexane); ^{1}H NMR (Me_2SO-d_6) δ 2.22 (s, C_2- and C_6CH_3), 2.35 (s, Ar CH_3), 3.23 (s, C_3- and C_5COOCH_3), 5.00 (s, C_4H), 7.4–7.6 (m, Ar H), 8.57 (s, NH), 8.87 (s, CH=N), 11.47 (s, $NHSO_2$).

B. Dimethyl 1,4,5,8-Tetrahydro-4,6-dimethyl-1,4,8-metheno-2,3,5-benzotriazecine-7,13α-dicarboxylate (13). A solution of 0.50 g (0.0015 mol) of **5** and 0.30 g (0.0016 mol) of tosylhydrazine in 50 mL of benzene was stirred at room temperature for 3 h. The precipitate that formed during the first hour redissolved on continued stirring. The benzene solution was washed twice with H_2O and was dried (Na_2SO_4). The benzene was removed at room temperature. The residue was dissolved in ethyl acetate and was precipitated by addition of hexane to give 0.35 g (68%) of **13**: TLC, single spot, R_f 0.56 (1:1 ethyl acetate–hexane); ^{1}H NMR δ 1.58 (s, C_4CH_3), 2.31 (s, C_6CH_3), 3.75 (s, OCH_3), 3.83 (s, OCH_3), 4.82 (s, NH), 4.84 (s, C_8H), 6.91 (s, CH), 7.15–7.65 (m, Ar H); mp 95 °C (gas evolution).

C. Dimethyl 1,2,3,6α-Tetrahydro-2,4-dimethyl-1,2,6-metheno-3-benzazocine-5,11α-dicarboxylate (17). A solution of 1.00 g (0.003 mol) of **5** and 0.60 g (0.0032 mol) of tosylhydrazine in 100 mL of benzene was stirred at room temperature for 3 h and then was refluxed for 1 h. The cooled solution was washed with a dilute solution of $NaHCO_3$, H_2O, and brine, dried ($MgSO_4$), filtered, and was evaporated. The resulting residue was then purified by flash chromatography (silica gel, 35% ethyl acetate in hexane) to afford 0.40 g of **17**. Recrystallization of this material from ethyl acetate–hexane gave 0.23 g (24%) of **17**: TLC, single spot, R_f 0.70 (1:1 ethyl acetate–hexane); mp 162–163.5 °C; IR 3280 (NH), 1720 (CO) cm^{-1}; ^{1}H NMR δ 1.63 (s, 3 H, C_2CH_3), 2.18 (s, 3 H, C_4CH_3), 2.76 (s, 1 H, CH), 3.74 (s, 3 H, OCH_3), 3.82 (s, 3 H, OCH_3), 4.16 (s, 1 H, NH), 5.25 (s, 1 H, $C_{6a}H$), 7.06–7.16 (m, 4 H, Ar H). Anal. Calcd for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47. Found: C, 69.16; H, 6.30; N, 4.36.

Dimethyl 1,2,3,6α-Tetrahydro-2,4-dimethyl-1,2,6-metheno-3-benzazocine-5,11α-dicarboxylate (17). A. From 13. A sample of **13** was melted in an oil bath at 125 °C. The residue was chromatographically identical with **17** prepared above.

B. From 12. A solution of 0.111 g (0.0002 mol) of **12** and 0.014 g (0.00025 mL) of KOH in 10 mL of CH_3OH containing 0.5 mL of H_2O was stirred at room temperature overnight. After evaporation, the residue was taken up in CH_2Cl_2, washed with H_2O, dried (Na_2SO_4), and evaporated to dryness. The residue was dissolved in benzene (20 mL) and was refluxed for 2 h. The solution was evaporated to dryness, and the residue was purified by flash chromatography (silica gel, 20% ethyl acetate in hexane). The product was chromatographically and spectrally identical by IR and NMR with **17** prepared by the direct reaction of tosylhydrazine with dimethyl 2,6-dimethyl-4-(2-formyl)phenyl-1,4-dihydropyridine-3,5-dicarboxylate (**5**).

Dimethyl 2,6-Dimethyl-4-[2-(1,3-dioxolan-2-yl)-4-methoxyphenyl]-1,4-dihydropyridine-3,5-dicarboxylate (3). A stirred mixture of **20**[25] (26.5 g, 0.123 mol), ethylene glycol (18.6 g, 0.30 mol), and *p*-toluenesulfonic acid monohydrate (0.30 g) in 200 mL of toluene was refluxed under a Dean-Stark water separator for 12 h. The cooled mixture was washed with H_2O and brine, and the solution then was dried (Na_2SO_4). Evaporation of the solvent afforded 31.92 g (100%) of 2-[2-(1,3-dioxalanyl)]-4-methoxybromobenzene.

To a cooled solution (−78 °C) of the above bromo compound (31.92 g, 0.123 mol) in 200 mL of THF was added dropwise 2.6M *n*-butyllithium (50 mL of hexane, 0.13 mol) at such a rate that $T \leq -65$ °C. After the addition was complete, the solution was stirred for an additional 0.5 h at −78 °C. *N*-Formylpiperidine (13.94 g, 0.123 mol) in 50 mL of THF was added dropwise. After being stirred an additional 1 h at −78 °C, the solution was allowed to warm to room temperature (about 3 h) and then was brought to pH 8 with 3 N HCl. Ether (500 mL) was added. This organic layer was washed with a standard solution of NH_4Cl, a saturated solution of $NaHCO_3$, and brine. The solution was dried (Na_2SO_4), filtered, and concentrated to dryness to afford 24.35 g (95%) of **21** as a clear oil; ^{1}H NMR δ 3.88 (s, 3 H, OCH_3), 4.07–4.17 (m, 4 H, OCH_2CH_2O), 6.44 (s, 1 H, O–CH–O), 6.9–7.9 (m, 3 H, Ar H), 10.23 (s, 1 H, CHO).

A solution of **21** (24.35 g, 0.117 mol), methyl acetoacetate (13.82 g, 0.12 mol), and methyl 3-aminocrotonate (13.92 g, 0.12 mol) in 100 mL of isopropyl alcohol was stirred at reflux under N_2 for 20 h. The cooled solution was concentrated under vacuum. The residue was crystallized from isopropyl alcohol–hexane to afford 12.62 g (27%) of **3**: mp 190.5–191.5 °C; ^{1}H NMR δ 2.46 (s, 6 H, CH_3), 3.79 (s, 6 H, CO_2CH_3), 3.89 (s, 3 H, OCH_3), 4.08–4.4 (m, 4 H, OCH_2CH_2O), 3.2 (s, 1 H, C_4N), 5.69 (s, 1 H, NH), 6.48 (s, 1 H, OCHO), 6.8–7.4 (m, 3 H, Ar H). Anal. Calcd for $C_{21}H_{25}NO_7$: C, 62.52; H, 6.25; N, 3.47. Found: C, 62.84; H, 6.58; N, 3.35.

Dimethyl 2,6-Dimethyl-4-(2-formyl-4-methoxyphenyl)-1,4-dihydropyridine-3,5-dicarboxylate (6). A solution of **3** (12.5 g, 0.031 mol) and *p*-toluenesulfonic acid monohydrate (0.40 g) in 450 mL of acetone was stirred at room temperature for 20 h. Methylene chloride was added to the residue after the acetone was removed by evaporation. The organic solution was washed with a dilute solution of sodium carbonate and brine and dried ($MgSO_4$). Evaporation of the solvent afforded 8.97 g (81%) of **6**, which was crystallized from ether–hexane: mp 176.5–178 °C; ^{1}H NMR δ 2.37 (s, 6 H, CH_3), 3.56 (s, 6 H, CO_2CH_3), 3.83 (s, 3 H, OCH_3), 5.65 (s, 1 H, NH), 5.70 (s, 1 H, C_4H), 7.0–7.4 (m, 3 H, Ar H), 10.88 (s, 1 H, CHO). Anal. Calcd for $C_{19}H_{21}NO_6$: C, 63.50; H, 5.89; N, 3.90. Found: C, 63.85; H, 6.29; N, 3.97.

Dimethyl 1,4,5,8-Tetrahydro-11-methoxy-4,6-dimethyl-1,4,8-metheno-2,3,5-benzotriazecine-7,13α-dicarboxylate (14). A solution of 0.36 g (0.001 mol) of **6** and 0.20 g (0.001 mol) of recrystallized tosylhydrazine in benzene (20 mL) was stirred at room temperature for 1 h. The solvent was removed under vacuum, and the product was purified by flash chromatography (silica gel; 35% ethyl acetate in hexane), followed by dissolving the residue in cold ethyl acetate and adding hexane to incipient crystallization to afford 0.17 g (46%) of pure crystalline **14**: mp 125 °C (with gas evolution); IR 3330 (NH), 1730, 1700 (CO) cm^{-1}; ^{1}H NMR δ 1.57 (s, 3 H, C_4CH_3), 2.30 (s, 3 H, C_6CH_3), 3.75 (s, 3 H, OCH_3), 3.82 (s, 3 H, OCH_3), 3.83 (s, 3 H, OCH_3), 4.75 (s, 1 H, C_8H), 4.78 (s, 1 H, NH), 6.82 (d, 1 H, $C_{10}H$), 6.83 (s, 1 H, C_1H), 7.08 (d, 1 H, C_9H), 7.14 (d, 1 H, $C_{12}H$). Anal. Calcd for $C_{19}H_{21}N_3O_5$: C, 61.44; H, 5.70; N, 11.32. Found: C, 61.47; H, 5.90; N, 11.49.

Dimethyl 1,2,3,6α-Tetrahydro-2,4-dimethyl-9-methoxy-1,2,6-metheno-3-benzazocine-5,11α-dicarboxylate (18). A

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solution of **6** (1.26 g, 0.0035 mol) and recrystallized tosylhydrazine (0.69 g, 0.0037 mol) in 50 mL of benzene was stirred at room temperature for 1 h. During this time, a solid crystallized from solution but then quickly redissolved. The solution then was refluxed for 1 h. The benzene solution was washed with H_2O and brine, dried ($MgSO_4$), filtered, and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 35% ethyl acetate in hexane) followed by recrystallization from ethyl acetate–hexane to afford 0.56 g (47%) of pure **18**: mp 160.5–162 °C; IR 3320 (NH), 1730 (CO) cm^{-1}; ^1H NMR δ 1.63 (s, 3 H, C_2CH_3), 2.18 (s, 3 H, C_4CH_3), 2.70 (s 1, C_1H), 3.74 (s, 3 H, OCH_3), 3.76 (s, 3 H, Ar OCH_3), 3.80 (s, 3 H, OCH_3), 4.18 (s, 1 H, NH), 5.16 (s, 1 H, C_6H), 6.6–7.0 (m, 3 H, Ar H). Anal. Calcd for $C_{19}H_{21}NO_5$: C, 66.46; H, 6.17; N, 4.08. Found: C, 66.50; H, 6.38; N, 3.97.

A sample of **14** was melted at 125 °C in an oil bath. The residue was chromatographically identical with **18** prepared by the above procedure.

3-Hydroxy-6-nitro-1-(3*H*)isobenzofuranone (23). A mixture of 8.89 g (0.050 mol) of **22**[26] and 8.9 g (0.050 mol) of *N*-bromosuccinimide in 135 mL of CCl_4 was stirred and heated under reflux for 1 h, during which time the reaction mixture was exposed to the light from a 275-W, 125-V Hanovia sunlamp that was situated 8 in. from the flask. After the mixture was cooled, the succinimide was removed by filtration, and the filtrate was evaporated in vacuo. The oily residue (10.17 g) was mixed with 200 mL of H_2O, and the mixture was refluxed for 1 h to give a clear, colorless solution. On cooling, 9.50 g (55%) of **23** crystallized from solution. An analytical sample was prepared by recrystallization from H_2O: mp 157–160 °C; IR 3390 (OH), 1770 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$–Me_2SO-d_6–D_2O) δ 6.78 (s, br, 1 H, C_3H), 7.88 (d, 1 H, C_4H, $J_{4,5}$ = 9 Hz), 8.56 (d, 1 H, C_5H, J = 9 Hz), 8.62 (s, 1 H, C_7H). Anal. Calcd for $C_8H_5NO_5$: C, 49.24; H, 2.58; N, 7.18. Found: C, 49.39; H, 2.58; N, 7.13.

2-[1,3-Dithian-2-yl]-5-nitrobenzoic Acid (24). To an ice-cooled mixture of **23** (5.00 g, 0.0256 mol) and propane-1,3-dithiol (2.92 g, 0.027 mol) in $CHCl_3$ (75 mL) was added 2 mL of BF_3·Et_2O. The mixture was stirred and allowed to warm to room temperature. After the mixture was stirred for 3 h, most of the solid had dissolved. Magnesium sulfate was added to dry the solution, and stirring was continued overnight. Filtration and evaporation of the solvent afforded a light yellow solid. This material was triturated with butyl chloride to give 6.38 g (87%) of **24**: mp 192–194 °C; ^1H NMR ($CDCl_3$–MeSO-d_6–D_2O) δ 1.8–2.3 (m, 2 H, $CH_2CH_2CH_2$), 2.9–3.2 (m, 4 H, $CH_2CH_2CH_2$), 6.56 (s, 1 H, SCHS), 7.6–8.8 (m, 3 H, Ar H). Anal. Calcd for $C_{11}H_{11}NO_4S_2$: C, 46.30; H, 3.89; N, 4.91. Found: C, 46.29; H, 3.84; N, 5.03.

2-[1,3-Dithian-2-yl]-5-nitrobenzyl Alcohol. To an ice-cooled, stirred solution of **24** (5.00 g, 0.0175 mol) in 100 mL of THF was added dropwise over 30 min 20 mL of 1.0 M BH_3·THF. The solution was allowed to warm to room temperature and was stirred overnight. An additional 5 mL of 1.0 M BH_3·THF was added, and the solution was stirred another 4 h. Water was added to hydrolyze the reaction, and the solution then was evaporated to dryness. The residue was dissolved in ether, and this solution was washed with a saturated solution of sodium carbonate and then brine and was dried over magnesium sulfate. Evaporation of the solvent and recrystallization of the product from acetonitrile afforded 4.47 g (94%) of 2-[1,3-dithian-2-yl]-5-nitrobenzyl alcohol: mp 130–131 °C; IR 3600 (OH) cm^{-1}; ^1H NMR ($CDCl_3$–D_2O) δ 1.8–2.2 (m, 2 H, $CH_2CH_2CH_2$); 2.8–3.2 (m, 4 H, $CH_2CH_2CH_2$), 4.61 (s, 2 H, CH_2O), 5.48 (s,] H, SCHS), 7.7–8.3 (m, 3 H, Ar H). Anal. Calcd for $C_{11}H_{13}NO_3S_2$: C, 48.69; H, 4.83; N, 5.16. Found: C, 49.03; H, 5.01; N, 5.01.

2-[1,3-Dithian-2-yl]-5-nitrobenzaldehyde. To a solution of 3.47 g (0.0128 mol) of 2-[1,3-dithian-2-yl]-5-nitrobenzyl alcohol in CH_2Cl_2 (100 mL) was added 4.15 g (0.0192 mol) of pyridinium chlorochromate. The mixture was stirred for 1 h, an additional 2.0 g of pyridinium chlorochromate was added, and the mixture was stirred 15 h. Ether (200 mL) was added to the reaction mixture, and the solvent was decanted and evaporated. The residue was purified by chromatography (silica gel, $CHCl_3$), affording 2.27 g (66%) of light yellow crystals: mp 99–101 °C; IR 1730 (C=O) cm^{-1}; ^1H NMR δ 1.7–2.3 (m, 2 H, $CH_2CH_2CH_2$), 2.8–3.3 (m, 4 H, $CH_2CH_2CH_2$), 6.13 (s, 1 H, SCHS), 7.8–8.7 (m, 3 H, Ar H), 10.45 (s, 1 H, CHO). Anal. Calcd for $C_{11}H_{11}NO_3S_2$: C, 49.05; H, 4.12; N, 5.20. Found: 49.16; H, 4.18; N, 5.60.

Dimethyl 4-(2-[1,3-Dithian-2-yl]-5-nitrophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (25). To a solution of 2-[1,3-dithian-2-yl]-5-nitrobenzaldehyde (2.27 g, 0.00843 mol) in 25 mL of CH_3OH were added 0.99 g (0.0085 mol) of methyl acetoacetate and 0.98 g (0.0085 mole of methyl β-aminocrotonate. The solution was stirred and refluxed for 24 h. The crystalline solid that formed during the reflux period was removed by filtration and was with methanol and dried to afford 2.13 g (54%) of **25**: mp 278–279 °C; IR 3435 (NH), 1695 (CO) cm^{-1}; ^1H NMR δ 1.9–2.3 (m, 2 H, $CH_2CH_2CH_2$), 2.37 (s, 6 H, CH_3), 2.8–3.3 (m, 4 H, $CH_2CH_2CH_2$), 3.64 (s, 6 H, OCH_3), 5.39 (s, 1 H, C 4H), 5.86 (s, 1 H, SCHS), 5.92 (s, 1 H, NH), 7.8–8.2 (m, 3 H, Ar H). Anal. Calcd for $C_{21}H_{24}N_2O_6S_2$: C, 54.29; H, 5.21; N, 6.03. Found: C, 54.20; H, 5.25; N, 6.13.

Dimethyl 4-(2-Formyl-5-nitrophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (7). To a vigorously stirred mixture of mercuric oxide (0.93 g, 0.0043 mol) and BF_3·Et_2O (0.612 g, 0.00431 mol) in 10 mL of 15% aqueous THF[27] was added dropwise over 10 min, a solution of **25** (1.00 g, 0.00215 mol) in 35 mL of THF. The mixture was stirred for 18 h at room temperature and then was refluxed for 15 min. The mixture was concentrated to dryness, and $CHCl_3$ was added to the residue. The mixture was filtered, and the filtrate was washed with a Na_2CO_3 solution and H_2O and was dried ($MgSO_4$). Evaporation of the solvent afforded 0.43 g (54%) of **7**.

An analytical sample of **7** was prepared by flash chromatography (silica gel, 35% ethyl acetate in hexane), followed by recrystallization from ethyl acetate–hexane: mp 233–236 °C; IR 3375 (NH), 1710, 1690, 1645 (CO) cm^{-1}; ^1H NMR δ 2.40 (s, 6 H, CH_3), 3.56 (s, 6 H, OCH_3), 5.83 (s, 1 H, C_4H), 6.00 (s, 1 H, NH), 7.7–8.3 (m, 3 H, Ar H), 10.65 (s, 1 H, CHO). Anal. Calcd for $C_{18}H_{18}N_2O_7$: C, 57.75; H, 4.84; N, 7.49. Found: C, 57.90; H, 4.88; N, 7.57.

Dimethyl 1,2,3,6α-Tetrahydro-2,4-dimethyl-8-nitro-1,2,6-metheno-3-benzazocine-5,11α-dicarboxylate (19). To a solution of 0.80 g (0.00214 mol) of **7** in 50 mL of benzene was added 0.418 g (0.00224 mol) of recrystallized tosylhydrazine. The solution was stirred under N_2 at room temperature. After about 30 min, a crystalline precipitate formed. After the mixture was stirred another 45 min, a homogeneous solution was obtained. The solution then was stirred for an additional 2 h at room temperature and for 16 h at reflux. The solvent was removed, and the residue was purified by flash chromatography (silica gel, 30% ethyl acetate in hexane), followed by recrystallization from ethyl acetate–hexane, to afford 0.196 g (26%) of pure **19**: mp 177–179 °C; IR 3310 (NH), 1710, 1640 (CO) cm^{-1}; ^1H NMR δ 1.68 (s, 3 H, C_2CH_3), 2.19 (s, 3 H, C_4CH_3), 2.80 (s, 1 H, C_1H), 3.77 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 4.21 (s, 1 H, NH), 5.35 (s, 1 H, C_6H), 7.8–8.1 (m, 3 H, Ar H). Anal. Calcd for $C_{18}H_{18}N_2O_6$: C, 60.33; H, 5.06; N, 7.82. Found: C, 60.48; H, 5.06; N, 7.96.

X-ray Crystal Structure Analysis of 16. Suitable crystals of **16** for X-ray diffraction studies formed from ethyl acetate–hexane mixtures with space group symmetry of *Pbca* and cell constants of a = 13.854 (3) Å, b = 14.237 (3) Å, and c = 18.575 (5) Å for Z = 8 and a calculated density of 1.347 g/cm^3. Of the 2464 reflections measured with an automatic four-circle diffractometer equipped with Cu radiation, 2039 were observed ($I \geq 3\sigma I$). The structure was solved with a multisolution tangent formula approach and difference Fourier analysis and refined with full-matrix least-squares.[28] Hydrogens were assigned isotropic temperature factors corresponding to their attached atoms. The function $\sum\omega(|F_o| - |F_c|)^2$ with $\omega = 1/(\sigma F_o)^2$ was minimized to give an unweighted residual of 0.062. No abnormally short intermolecular contacts were noted. Tables I, II, and III containing the final fractional coordinates, temperature parameters, bond distances, and bond angles are available as supplementary material.

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X-ray Crystal Structure Analysis of 14. Suitable crystals of 14 formed from ethyl acetate–hexane mixtures with space group symmetry of $P\bar{1}$ and cell constants of a = 9.699 (2) Å, b = 12.688 (4) Å, c = 8.122 (3) Å, α = 96.41 (3)°, β = 110.88 (2)°, and γ = 77.74 (2)° for Z = 2 and a calculated density of 1.353 g/cm^3. Of the 2503 reflections measured with an automatic four-circle diffractometer equipped with Cu radiation, 2138 were observed ($I \geq 3\sigma I$). The function $\sum\omega(|F_o| - |F_c|)^2$ was minimized to give an unweighted residual of 0.057. Tables IV, V, and VI containing the final fractional coordinates, temperature parameters, bond distances, and bond angles are available as supplementary material.

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Registry No. 1, 96557-29-8; 2, 98014-99-4; 3, 98015-09-9; 4, 98015-00-0; 5, 96575-49-4; 6, 98015-10-2; 7, 98015-17-9; 8, 98015-01-1; 9, 98015-03-3; 12, 98015-06-6; 13, 98015-04-4; 14, 98015-11-3; 16, 98015-02-2; 17, 98015-05-5; 18, 98015-12-4; 19, 98015-18-0; 20, 7507-86-0; 21, 98015-08-8; 22, 610-93-5; 23, 77619-93-3; 24, 98015-13-5; 25, 98015-16-8; ethylene glycol, 98015-07-7; methyl acetoacetate, 105-45-3; methyl 3-aminocrotonate, 14205-39-1; 2-[1,3-dithian-2-yl]-5-nitrobenzyl alcohol, 98015-14-6; 2-[1,3-dithian-2-yl]-5-nitrobenzaldehyde, 98015-15-7.

Supplementary Material Available: Tables of the atomic positional and thermal parameters, bond distances, and bond angles for 14 and 16 (10 pages). Ordering information is given on any current masthead page.

A Comparison of Single- and Dual-Parameter Equations in the Correlation of Carbon-13 Shifts in Substituted Styrenes

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^{13}C chemical shifts of β-carbon atoms in 17 series of substituted styrenes have been used to establish σ^{13} substituent constants for nine para and seven meta substituents. The σ^{13} values are similar to σ^+ values for electron-donating substituents, but are somewhat elevated for the cyano and nitro groups in both meta and para positions. Despite this, the use of mixed constants, σ^+ for electron donors and σ^- for electron withdrawers, does not enhance the correlations. In dual substituent parameter (DSP) treatments, Swain's field and resonance parameters, F and R, give very slightly better correlations than do Taft's parameters, σ_I and any one of the four standard σ_R scales. The Swain and Taft approaches agree closely on the relative amounts of electron supply and demand through resonance and field effects. The σ^{13} scale based on β-carbon shifts fails completely to correlate the shifts of the α-carbon atoms. In this case, Swain's parameters are clearly superior to any combination of the Taft sets. These results suggest that, at least for the 289 compounds comprising the data set reported here, the use of multiple resonance scales in DSP treatments is perhaps unjustified.

The number of observations that ^{13}C chemical shifts in various series of substituted benzenes correlate well with Hammett-type substituent constants is sufficient to suggest that the use of shift data can provide a convenient way to determine such constants.[1-8] Despite this, attempted correlations of shifts of the carbons in an aromatic ring are sometimes unsatisfactory,[9] perhaps because of substituent anisotropies that are not handled by the usual substituent constants. Consequently, attention has been directed toward substituted styrenes,[3-5,8,10-17] in which the side-chain carbons are far enough removed from the substituents to minimize anisotropic effects yet electrical effects can still be reliably transmitted to them by virtue of extended conjugation. In these series, the chemical shifts of α-carbon atoms typically show a very narrow range and a "reverse" correlation that is interpretable in terms of substituent-induced charge alternation throughout the carbon skeleton.[14] Those of the β-carbons, however, usually show a fairly wide range and an excellent correlation of expected

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