H, Ar H). Found: C, 55.70; H, 5.09.

3h: mp 208–210 °C (from Et_2O), $[\alpha]_D$ −9.1° (*c* 1, $CHCl_3$); ^1H NMR δ 1.33 (3 H, s, CH_3), 1.51 (3 H, s, CH_3), 1.88 (1 H, dd, *J* = 12 and 3.5 Hz, H-1′a), 2.23 (1 H, dd, *J* = 12 and 5.5 Hz, H-1′b), 2.72 (1 H, d, *J* = 4.5 Hz, OH), 3.21 (1 H, dd, *J* = 10 and 6 Hz, H-6a), 3.37 (1 H, dd, *J* = 10 and 3 Hz, H-6b), 3.76 (1 H, dt, *J* = 4.5, 4.5, and 2 Hz, H-2), 4.03 (1 H, dd, *J* = 7 and 6 Hz, H-4), 4.16 (1 H, dt, *J* = 6, 6, and 3 Hz, H-5), 4.22 (1 H, dd, *J* = 7 and 4.5 Hz, H-3), 4.32 (1 H, ddd, *J* = 5.5, 3.5, and 2 Hz, H-1), 7.3 (15 H, Ar H). Found: C, 55.68; H, 5.22.

Reactivity of 7,12-Dihydropyrido[3,2-*b*:5,4-*b*′]diindole with Electrophilic Reagents. Experimental and Computational Results

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Received March 10, 1988

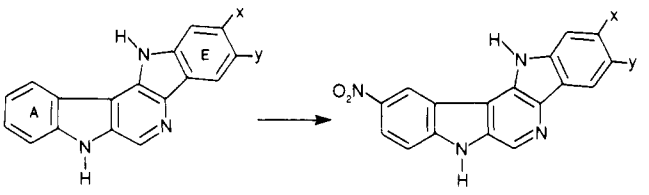
The reactivity of 7,12-dihydropyrido[3,2-*b*:5,4-*b*′]diindole (**1**) toward a variety of electrophiles ($^+NO_2$, Br^+, Cl^+, HSO_3^+) in acidic media has been investigated. Electrophilic attack on the protonated species **11** results in substitution at position 10 with high regioselectivity [i.e. **11** → **10** (92%), **11** → **13** (>73%)], effectively differentiating between the benzene nuclei, ring A and ring E of **1**. Attack of an electrophile (Br_2, HOAc/NaOAc) on the neutral molecule **1** results in a mixture of mono- and polysubstituted derivatives as predicted by MNDO calculations. The results of these electrophilic substitution reactions were compared to the p_z electron density populations and π-localization energies for the transition-state σ-complexes obtained from MNDO calculations. The experimental and theoretical results were in satisfactory agreement.

The heterocyclic base 7,12-dihydropyrido[3,2-*b*:5,4-*b*′]-diindole **1** was first reported in 1985.[1] It was later found that **1** possesses high affinity for the benzodiazepine receptor site in vitro and exhibits a broad range of biological profiles when the E-ring of the heterocycle is substituted with various functional groups.[2] These pyridodiindoles are the first completely rigid, planar benzodiazepine receptor ligands to have been prepared and provide a powerful tool with which to probe the topography of these receptors. It was, therefore, of interest to examine the reactivity of this heterocycle toward electrophiles and ultimately develop chemistry in which electrophiles could be introduced regioselectively, differentiating between the seemingly chemically similar benzene nuclei (ring A or E) of **1**. This would provide an entry into new, biologically active, high affinity ligands with which to further probe the pharmacophore of the benzodiazepine receptor.[3]

Results and Discussion

The synthesis of the pyridodiindoles is based on the Fischer–indole cyclization, as outlined in Scheme I. Treatment of the keto amide **2**[1] with phenylhydrazine at 160 °C followed by the concomitant [3,3] sigmatropic rearrangement[4] provided the diindole **3**, as illustrated. Cleavage of the benzoyl function of **3** with hydrazine, followed by an oxidation–disproportionation reaction across the 5–6 bond of the intermediate diindole **4** generated the fully aromatic pyridodiindoles in yields ranging from 50% and 88%. The process is illustrated for the 3-chloro (**5**)[5] and 3-bromo (**6**) analogues, respectively, in Scheme I.

Table I. Products of Nitration



1, x = H, y = H
5, x = H, y = Cl
8, x = Cl, y = H

10, x = H, y = H
7, x = H, y = Cl
9, x = Cl, y = H

compd	$NO_2(g)$/HNO_3[a]	70% HNO_3 (25 °C)	NO_2BF_4 (50 °C)	$NaNO_2$/TFA (25 °C)
1	PN	PN[a]	NR[a]	**10**, 92%[a]
5	PN	**7**, 67%	NR	**7**, 80%
8	PN	**9**, 66%	NR	**9**, 94%

[a] Reaction temperature = 0 °C; PN = polynitration products; NR = no reaction.

Since the 7,12-dihydropyrido[3,2–*b*:5,4–*b*′]diindole (**1**) has two para (3 and 10) and two ortho (1 and 8) positions with respect to the indole nitrogen atoms, which could undergo electrophilic attack, initial studies were directed toward the reactivity of the 3-chloro derivative **5**. The chlorine atom serves to block the 3-position from electrophilic attack, as well as deactivate ring E toward reaction with electrophiles.

Nitration. The 3-chloropyridodiindole **5** was stirred in a mixture of concentrated nitric acid/fuming nitric acid at 0 °C analogous to the conditions employed for the mononitration of 3-(alkoxycarbonyl)-β-carbolines at position 6.[6] This resulted in an inseparable mixture of

(1) Fukada, N.; Trudell, M. L.; Johnson, B.; Cook, J. M. *Tetrahedron Lett.* **1985**, *26*, 2139–2142.

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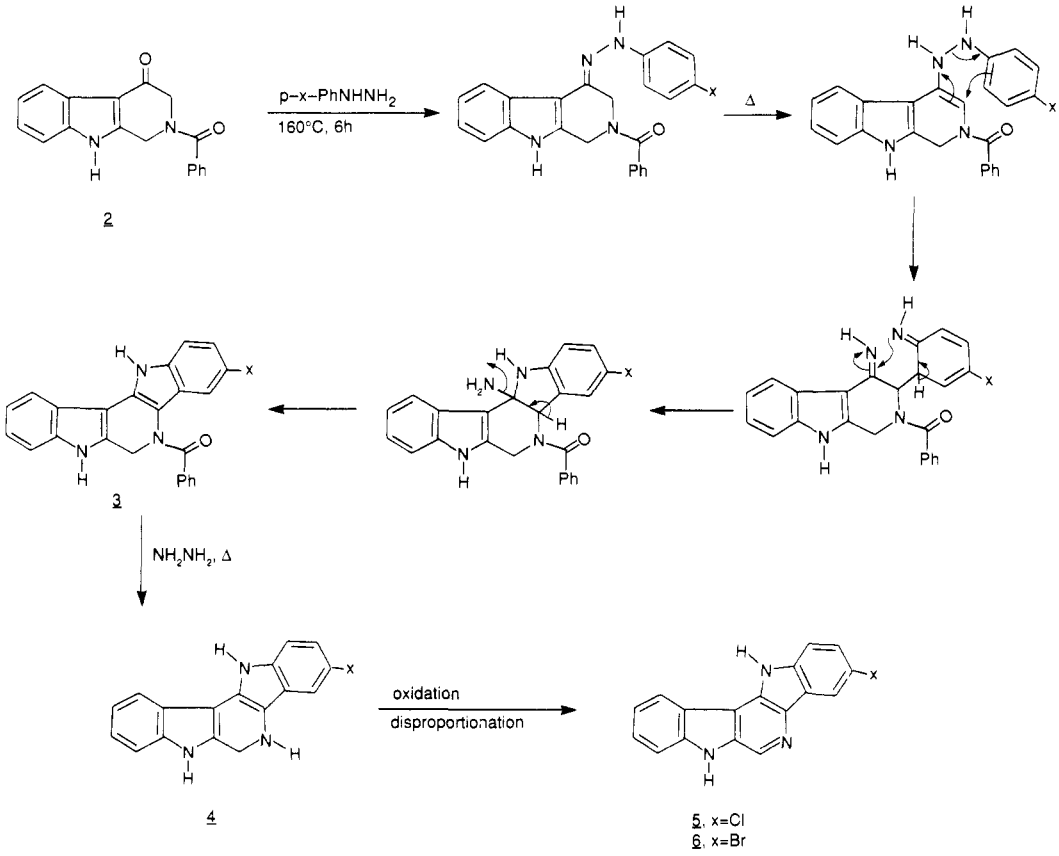
(3) Hagen, T. J.; Skolnick, P.; Shannon, H. E.; Cook, J. M. *Abstracts of Papers*, 20th Great Lakers Regional of the American Chemical Society, Milwaukee, WI, 1986, American Chemical Society: Washington, DC, 1986; Abstract 262. Hagen, T. J.; Trudell, M. L.; Lifer, S. L.; Tan, Y-C.; Allen, M. S.; Skolnick, P.; Codding, P.; Cook, J. M. *Abstracts of Papers*, 43rd Southwwest Regional Meeting of the American Chemical Society, Little Rock, AR, 1987; American Chemical Society: Washington, DC, 1987; Abstract MED 214.

(4) Crooks, P. A.; Robinson, B. *Chem. Ind. (London)* **1967**, 547. Kelly, A. H.; Panick, J. *Can. J. Chem.* **1966**, *44*, 2455–2460.

(5) Trudell, M. L.; Fukada, N.; Cook, J. M. *J. Org. Chem.* **1987**, *52*, 4293–4296.

0022-3263/88/1953-4185$01.50/0

Scheme I



products which included mononitro- and dinitrochloropyridodiindoles. It became necessary to employ milder conditions to effect mononitration. Treatment of **5** with 70% nitric acid at room temperature afforded the desired 3-chloro-10-nitropyridodiindole **7** in 67% yield (Table I). In similar fashion, the 2-chloro-10-nitropyridodiindole **9** was prepared in 66% yield from the 2-chloropyridodiindole **8**. Although concentrated nitric acid proved to be a suitable reagent for the mononitration of **5** and **8**, it was found inappropriate to selectively effect the mononitration of the parent pyridodiindole **1**.

The nitration of aromatic compounds,[7] as well as nitrogen-containing heterocycles,[8] employing nitronium tetrafluoroborate (NO_2BF_4) has been extensively investigated and found to take place readily. However, when **1** was stirred with NO_2BF_4 in sulfolane or methanol, no products of nitration were observed.

Sodium nitrite in trifluoroacetic acid (TFA) has been found to be a mild nitrating agent which provides a wide variety of nitroamines in high yield.[9] The regioselective nature of this reagent had been previously demonstrated in our laboratories in the 1,6-diazaphenalene area.[10] When the pyridodiindole **1** was reacted with 1.6 equiv of $NaNO_2$ in TFA, a 92% yield of the desired 10-nitropyridodiindole **10** was realized. This nitration process was subsequently employed for the preparation of the 10-nitrochloro derivatives **7** and **9** in high yield. More importantly, the use of $NaNO_2$/TFA provided a means by which to differentiate between rings A and E of the pyridodiindole (**1**) system. The results of the nitration reactions are summarized in Table I.

Table II. Electron Population Densities

	1			11		
atom	net atomic charge	HOMO	p_z	net atomic charge	HOMO	p_z
Cl	−0.0949	0.055	0.479	−0.0750	0.043	0.488
C2	−0.0236	0.049	0.463	−0.0186	0.059	0.444
C3	−0.1036	0.007	0.509	−0.0665	0.001	0.490
C4	0.0228	0.070	0.452	0.0139	0.047	0.464
N5	−0.1540			−0.0499		
C6	−0.0022	0.149	0.280	0.0643	0.084	0.415
N7	−0.2482			−0.2260		
C8	−0.0891	0.031	0.451	−0.0822	0.069	0.490
C9	−0.0238	0.004	0.435	0.0216	0.009	0.443
C10	−0.0956	0.052	0.477	−0.0719	0.143	0.495
C11	0.0017	0.005	0.433	0.0209	0.047	0.455
N12	−0.2559			−0.2268		

The regiospecificity observed for the nitration of **1** is interesting. In order to obtain a better understanding of the observed regiochemistry of the nitration process, the electronic structure of this aromatic base was examined. The net atomic charge densities were calculated for geometry optimized structures by using MNDO[11] (Table II). Since the nitration reactions were performed in acidic media the net atomic charge densities were calculated for the protonated species **11**/**1**–(5 H^+), as well as for the free base **1**. The results of the MNDO calculation on **11** in-

(6) Neef, G.; Eder, V.; Huth, A.; Rahtz, D.; Schmiechen, R.; Seidelman, D. *Heterocycles* **1983**, *21*, 1295–1313.
(7) Kuhn, S. J.; Olah, G. *J. Am. Chem. Soc.* **1961**, *83*, 4564–4571, 4571–4581, 4581–4585.
(8) Cupas, C. A.; Pearson, R. L. *J. Am. Chem. Soc.* **1968**, *90*, 4742–4746.
(9) Vemura, S.; Toshimitsu, A.; Okano, M. *J. Chem. Soc., Perkin Trans. 1* **1978**, 1076–1079.
(10) Lee, S.-J. MS Thesis, University of Wisconsin—Milwaukee, 1984. Lee, S.-J.; Cook, J. M. *Heterocycles* **1983**, *20*, 87–111.
(11) (a) Dewar, M. J. S.; Theil, W. *J. Am. Chem. Soc.* **1977**, *99*, 4899–4907. (b) The QCPE program was expanded to a 50-atom capability: Sorensen, T.; England, W. B., unpublished results.
(12) Fukui, K.; Yonezawa, T.; Nagata, O. *Bull. Chem. Soc. Jpn.* **1954**, *27*, 423–429.

Table III. Reaction of 1 (11) with NBS in CH_2Cl_2/TFA

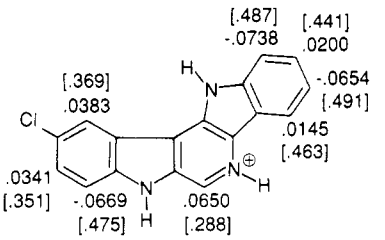
equiv of NBS	T, °C	1[a]	13[a]	14a	tribromo[b]	tetra-bromo[b]	penta-bromo[b]
1	25	17	75	8			
1	0	30	61	8			
1	−20	67	26	4			
2	25		4	96			
3	25		2	65	26	5	
4	25				31	24	6
10	25				47	41	12

[a] Composition (%) based on analysis by HPLC. [b] See ref 15.

dicate that the net atomic charge densities of the carbon atoms decrease in the order 8 > 1 > 10 > 3 > others (Table II), which suggests that position 8 (−0.0822) should be the most susceptible to electrophilic attack. The order of net atomic charge densities of the carbon atoms of the free base 1 decreases in the order 3 > 10 > 1 > 8 > others (Table II). In both cases, the net atomic charge densities do not correlate with the observed reactivity. Moreover, population densities of the highest occupied molecular orbitals (HOMO) of 1 and 11 (Table II) did not provide any better correlation to the observed experimental results.

In electrophilic aromatic substitution reactions, electrophiles attack the electron-rich π-cloud of an aromatic system, forming an intermediate σ-complex. It seemed reasonable, therefore, to examine the total p_z population density at a particular carbon atom in order to predict the reactivity of said position toward an electrophile. This approach provided more reasonable data (Table II) with a better correlation to the experimental results. The highest amount of p_z electron density for the protonated diindole **11** was found to reside at position 10 (0.495), with only slightly less located at position 8 (0.490) and at position 3 (0.490). This slight difference in p_z electron density did not seem significant enough to explain the observed regiochemistry. In order to further quantify the difference in reactivity between position 10 and position 8, the relative π-localization energies were calculated for the σ-complex transition state by utilizing the Wheland model for electrophilic aromatic substitution.[13] The π-localization energies for H^+ (the attacking electrophile) indicate that substitution at position 10, to form σ-complex **12a**/**1**–(5 H^+)(10 H^+), is favored over substitution at position 8, to form σ-complex **12b**/1–(5 H^+)(8 H^+), by 0.44 kcal/mol. The transition-state energy calculated for **12a** is lower than that calculated for **12b** due probably to the greater distance between the positive charge in ring A and on N(5) in transition state **12a** as compared to **12b**. Therefore, electrophilic substitution is favored at position 10 over position 8, which is in agreement with the experimental observations.

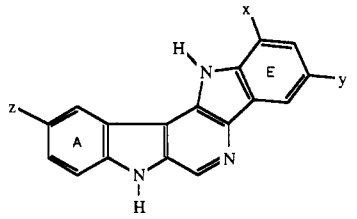
Halogenation. Since the observed regiochemistry of the nitration reaction could be understood via MNDO calculations, attention turned toward the halogenation of 1. The regiospecific bromination of 1,6-diazaphenalene is known to occur with 1 equiv of *N*-bromosuccinimide (NBS) in CH_2Cl_2/TFA.[14] By analogy to the previous reactivity of the protonated species 11, the bromination of 1 was predicted to occur at position 10 with high regioselectivity. Upon treatment of 1 with 1 equiv of NBS in CH_2Cl_2/TFA at room temperature, the 10-bromopyridodiindole **13** was obtained in 73% yield. In addition, a small amount of the 3,10-dibromopyridodiindole **14** (8%) and recovered 1 (17%) were realized. To ensure complete



15

Figure 1. Net atomic charge densities [p_z population densities].

consumption of starting pyridodiindole, 1 was reacted with a onefold excess of NBS, under conditions analogous to those described above. This procedure gave the 3,10-dibromopyridodiindole **14**, in 96% yield with only a trace of the 10-bromo derivative **13** (4%) present. When a larger excess of NBS was employed, polybrominated pyridodiindoles predominated.[15] The results of the bromination reaction (NBS) in CH_2Cl_2/TFA are summarized in Table III.



1,	x=y=z=H	17,	x=H, y=Cl, z=Cl
13,	x=H, y=H, z=Br	18,	x=Cl, y=H, z=Cl
14,	x=H, y=Br, z=Br	19,	x=H, y=NaO_3S, z=NaO_3S

The experimental results for the regioselective monobromination of 1 are in agreement with the calculations obtained for the reaction of 1 with electrophiles in acidic media. Again, reaction has been directed toward ring A rather than ring E of 1. It is important to note that the addition of a second bromine atom occurs at position 3, regioselectively, to provide **14**. The selectivity of the second electrophile can be understood upon examination of the electronic effects imposed by a halogen atom (Cl)[16] at position 10 of the molecule. The net atomic charge densities (Figure 1) are significantly lower in ring A than in ring E, due to the inductive effect of halogen. The p_z electron population densities of the 10-monohalogenated derivative **15** (Figure 1) indicate there is little electronic difference between position 3 (0.491) and position 1 (0.487). However, the π-localization energies calculated for the respective transition-state σ-complexes indicate that electrophilic attack at position 3, to form σ-complex **16a**/**15**–(5 H^+)(3 H^+), is favored over attack at position 1, to form σ-complex **16b**/**15**–(5 H^+)(1 H^+), by 4.39 kcal/mol.

The electrophilic chlorination of 1 was attempted under similar conditions to those employed in the reaction with bromine; however, only a small amount of chlorinated material was obtained. The reaction mixture was composed of starting pyridodiindole 1 (71%), accompanied by a complex mixture of monochloropyridodiindole derivatives which could not be resolved. Reaction of 1 with excess NCS gave only 3,10-dichloropyridodiindole **17**

(13) Wheland, G. W. *J. Am. Chem. Soc.* **1964**, *64*, 900–908.
(14) Weber, R. W.; Lee, S.-J.; Milosevich, S.; England, W. B.; Cook, J. M. *Can. J. Chem.* **1982**, *60*, 3049–3054.
(15) The tribromo-, tetrabromo-, and pentabromopyridodiindole derivatives were observed only by mass spectroscopy and HPLC. The yields are approximated from the HPLC analysis.
(16) The chlorine atom was employed in place of bromine because the MNDO calculation was not parameterized for Br.

Table IV. Bromination Reactions of 1 in HOAc/NaOAc

equiv	1[a]	13[a]	6[a]	14[a]	dibromo[b]	tribromo[c,d]	tetrabromo[c,d]
Br_2							
1	41	12	10	15	17	5	
2	11	4	8	36	12	28	
3		2		3	1	98	2
4				5		80	15
10						44	56
NBS							
1	47	20	7	12	8	6	

[a] Composition (%) determined by HPLC. [b] Mixture of isomers different than 14. [c] See ref 15. [d] Complex mixture of isomers which could not be resolved.

(30%) and 1,10-dichloropyridodiindole 18 (21%). The structures of 17 and 18 were determined by spectroscopy, moreover, the structure of 17 was confirmed by independent synthesis; the 3-chlorodiindole 5 prepared by an unambiguous route[5] was treated with NCS (1 equiv) to provide 17.

The apparent lesser reactivity and selectivity of the chlorinating reagent (NCS), as compared to NBS, may be due to the fact that the N–Cl bond is stronger than the N–Br bond in the reagent. The reaction conditions employed herein may not have been conducive to formation of the necessary electrophile from NCS. However, once Cl^+ has been generated it is much less selective[17] than Br^+ which results in complex product mixtures.

Sulfonation. Although many of the pyridodiindoles exhibit potent activity at benzodiazepine receptors, their future as drug candidates depends to some degree on their solubility in aqueous media.[18] It was felt that incorporation of a sulfonic acid moiety via electrophilic sulfonation should generate a more water-soluble compound. When the parent pyridodiindole 1 was stirred in concentrated sulfuric acid, disulfonation took place to provide the disulfonic acid. Conversion of the diacid into the disodium salt rendered handling and purification easier to provide 19 in 80% yield from 1. Attempts to prepare the monosulfonic acid derivative were unsuccessful. Only an inseparable mixture of the 10-pyridodiindolesulfonic acid sodium salt[19] and 19 was obtained.

While it is clear that electrophiles preferentially attack the protonated species 11 at position 10, reaction of the nonprotonated, free base 1 with electrophiles remained to be investigated. The bromination of imidazoles[20] and 1,6-diazaphenalenes,[10,12] as their conjugate bases, has been accomplished in glacial acetic acid in the presence of a large excess of sodium acetate.[21] The excess base is present to scavenge the hydrogen bromide formed in the bromination process, which prevents protonation of N(5). When 1 was stirred with 1 equiv of bromine in glacial acetic acid/sodium acetate, several brominated pyridodiindoles were formed. Analysis of the mixture by HPLC and mass spectrometry indicated the presence of 3-bromopyridodiidole 6 (10%), 10-bromopyridodiindole 13 (12%), and 3,10-dibromopyridodiindole 14 (15%), as well as 1 (41%) and other polybrominated materials. The analogous reaction was then repeated with NBS as the reagent to determine if the reaction medium (compare reaction in CH_2Cl_2/TFA, Table III) was responsible for the altered regiochemistry of the process rather than the brominating agent. In fact, the product distribution from the NBS process (Table IV) was very similar to that observed with bromine (Table IV) but substantially different from the TFA/NBS reaction (Table III). It was clear that the free base 1 was undergoing reaction with Br^+ in a manner different from the protonated species 11. Upon examination of the p_z population densities of the free base 1 (Table II), it is evident that position 3 (0.509) possesses a significantly greater amount of p_z density than position 10 (0.477), which suggests that position 3 should be more susceptible to electrophilic attack than position 10. Also upon comparison of the π-localization energies, electrophilic substitution at position 3, to form σ-complex **20a**/1-(3 H^+), is favored over substitution at position 10, to form σ-complex **20b**/1-(10 H^+), by 2.77 kcal/mol. Consequently, an approaching electrophile (Br^+) should exhibit a preference for attack at position 3 over position 10. The increased stability of the 3-substituted σ-complex **20a** leads to the formation of a greater amount of the 3-bromopyridodiindole 6 than observed under acidic reaction conditions. Therefore, under neutral reaction conditions complete loss of regioselectivity is observed, experimentally, wherein the 3-substituted derivative 6 and the 10-substituted derivative 13 are formed in nearly equal amounts (see the ratios of 6:13:14 depicted in Table IV).

Although regioselectivity is nearly nonexistent in the reaction of the free base 1 with electrophiles (Table IV), comparison of the p_z electron densities and π-localization energies of the corresponding σ-complexes of 1 and 11 permit one to selectively direct electrophilic attack to position 10 of 1 by executing the reaction in strong acid (see Tables I and III). Effectively, by protonation of N(5) this process differentiates between ring A and E of 1 and is consistent with the results of MNDO calculations.

The ability to execute electrophilic substitution, regioselectively, at position 10, when coupled with previous work,[5] permits the selective functionalization of 1 at positions 1, 2, 3, 4, or 10. Determination of the disposition of electron densities and the reactivity of this rigid, planar pyridodiindole 1 will prove invaluable in the design of new agents with which to probe the topography of benzodiazepine receptor binding sites.

Experimental Section

Microanalyses were performed on a F and M Scientific Corp. Model 185 carbon, hydrogen, and nitrogen analyzer. Melting points were recorded on a Thomas-Hoover melting point apparatus and are uncorrected. ^1H NMR spectra were recorded on a Bruker 250-MHz multiple-probe spectrometer. IR spectra were taken on either a Beckman Acculab-1, a Nicolet MX-1, or a Mattson Polaris IR-10400 spectrometer. Low-resolution mass spectral data (EI/CI) were obtained on a Hewlett-Packard 5855 GC–mass spectrometer, while high-resolution mass spectra were taken on a Finnigan HR mass spectrometer. Analytical TLC plates used were E. Merck Brinkmann UV-active silica gel. High-pressure liquid chromatography was run on a Waters Associates HPLC equipped with the following: Waters automated gradient controller; Waters Model M-45 solvent delivery system; Waters Model 6000A solvent delivery system; Waters C_{16} μ-Bondapak Column; Waters Model 440 absorbance detector. Unless otherwise stated, all chemicals were purchased from Aldrich Chemical Co.

Compounds 1, 5, and 6 were prepared by using procedures described in ref 5.

3-Chloro-7,12-dihydropyrido[3,2-*b*:5,4-*b*']diindole (5): mp >350 °C; IR (KBr) 3440, 3150, 2800, 1620, 1470 cm^{-1}; MS (CI, CH_4), m/e 292 (M + 1); ^1H NMR (DMSO-d_6) δ 12.41 (s, 1 H), 12.13 (s, 1 H), 8.92 (s, 1 H), 8.76 (d, 1 H, J = 7.9 Hz), 8.20 (d, 1

(17) For a comprehensive review, see: Stock, L. M.; Brown, H. C. *Adv. Phys. Org. Chem.* **1963**, *1*, 35–154.

(18) The partition coefficient of 7,12-dihydropyridodiindole 1 is equal to log $P_{oct/water}$ = 3.87. Trudell, M. L.; Martin, M. J.; Cook, J. M., unpublished results.

(19) The monosulfonic acid salt was observed by ^1H NMR and/or mass spectrometry.

(20) Stensio, K.; Whalberg, K.; Wahren, R. *Acta. Chem. Scand.* **1973**, *27*, 2174–217.

(21) $K_s = 3.5 \times 10^{-15} = [^+H_2OOCCH_3][CH_3COO^-]$, under the reaction conditions $[^+H_2OOCCH_3] = 8.75 \times 10^{-16}$ mol/L.

H, J = 2.0 Hz), 7.7 (d, 1 H, J = 8.6 Hz), 7.36 (t, 1 H, J = 7.2 Hz); exact mass calcd for $C_{17}H_{10}N_3Cl$ 291.0563, found 291.0548.

Anal. Calcd for $C_{17}H_{10}N_3Cl$: C, 69.99; H, 3.43; N, 14.41; Found: C, 69.90; H, 3.44; N, 14.41.

3-Bromo-7,12-dihydropyrido[3,2-*b*:5,4-*b*']diindole hydrochloride (6): mp >300 °C; MS (CI, CH_4), m/e (relative intensity) 257, (100), 335 (39.9), 336 (67.6), 337 (59.5), 338 (70.1), 339 (13.6); ^{1}H NMR (DMSO-d_6) δ 13.10 (s, 1 H), 12.79 (s, 1 H), 9.30 (s, 1 H), 8.90 (d, J = 8.25 Hz, 1 H), 8.65 (s, 1 H), 7.86 (t, J = 8.20 Hz, 1 H), 7.78 (d, J = 5.25 Hz, 1 H), 7.77 (d, J = 5.00 Hz, 1 H), 7.55 (t, J = 7.00 Hz, 1 H); exact mass calcd for $C_{17}H_{10}N_3Br$ 335.0058, found 335.0060.

Anal. Calcd for $C_{17}H_{10}N_3Br{\cdot}HCl{\cdot}^1/_2H_2O$; C, 51.08; H, 3.43; N, 10.52. Found: C, 50.67; H, 3.07; N, 10.51.

Nitration of Pyridodiindoles with Nitric Acid (Representative Procedure). 3-Chloro-10-nitro-7,12-dihydropyrido[3,2-*b*:5,4-*b*']diindole (7). The 3-chloropyridodiindole **5**[5] (0.1048 g, 0.359 mmol) was finely powdered and added to concentrated HNO_3 (10 mL, 70%) at 25 °C. The reaction was stirred vigorously for 1.5 h, after which the reaction was quenched with cold water (100 mL). The solution was adjusted to pH 8 with NH_4OH (concentrated). The precipiate which formed was filtered and dried (air). The dark red solid was added to methanol (25 mL) and stirred for 1 h after which the solid was filtered and dried (air) to yield **7** (0.0808 g, 67%): mp >300 °C; IR (KBr) 3344, 1473, 1330 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 7.45 (d of d, 1 H, J_{2-1} = 8.6 Hz, J_{2-4} = 2.0 Hz), 7.63 (d, 1 H, J_{1-2} = 8.5 Hz), 7.77 (d, 1 H, J_{8-9} = 9.1 Hz), 8.12 (d, 1 H, J_{4-2} = 1.8 Hz), 8.40 (d of d, 1 H, J_{9-8} = 9.0 Hz, J_{9-11} = 2.2 Hz), 8.89 (s, 1 H), 9.70 (d, 1 H, J_{11-9} = 2.0 Hz), 12.57 (s, 1 H), 12.68 (s, 1 H); exact mass calcd for $C_{17}H_9N_4O_2Cl$ 336.0414, found 336.0422.

2-Chloro-10-nitro-7,12-dihydropyrido[3,4-*b*:5,4-*b*']diindole (9): see Table 1 for conditions; 80%; mp >300 °C; IR (KBr) 3350, 1470, 1340 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 7.31 (d of d, 1 H, J_{3-4} = 8.4 Hz, J_{3-1} = 1.6 Hz), 7.56 (d, 1 H, J_{1-3} = 1.3 Hz), 7.79 (d, 1 H, J_{8-9} = 9.2 Hz), 8.17 (d, 1 H, J_{4-3} = 8.4 Hz), 8.42 (d of d, 1 H, J_{9-8} = 9.2 Hz, J_{9-11} = 2.2 Hz), 9.02 (s, 1 H), 9.60 (d, 1 H, J_{11-9} = 1.9 Hz), 12.81 (s, 1 H), 12.92 (s, 1 H); exact mass calcd for $C_{17}H_9N_4O_2Cl$ 336.0414, found 336.0399.

Nitration of Pyridodiindoles with $NaNO_2$/TFA (Representative Procedure). 10-Nitro-7,12-dihydropyrido[3,2-*b*:5,4-*b*']diindole (10). The base **1** (0.1089 g, 0.423 mmol) was suspended in trifluoroacetic acid (30 mL) and cooled to 0 °C (NaCl/ice). Sodium nitrite (0.0432 g, 0.626 mmol) was added to the yellow-colored mixture in one portion, at which time the solid dissolved. The red solution was stirred at 0 °C until the presence of starting material was no longer observed by TLC (SiO_2, EtOAc). The volume was reduced in vacuo and the residue taken up in water and brought to pH 8 with NH_4OH (concentrated). The solid nitro derivative was filtered and dried (air) to provide **10** (0.1178 g, 92%): mp >300 °C; IR (KBr) 3350, 1519, 1366 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 7.30 (t, 1 H, $J_{3-2(4)}$ = 7.4 Hz), 7.49 (t, 1 H), $J_{2-1(3)}$ = 7.5 Hz), 7.69 (d, 1 H, J_{1-2} = 8.0 Hz), 7.81 (d, 1 H, J_{8-9} = 9.1 Hz), 8.22 (d, 1 H, J_{4-3} = 7.7 Hz), 8.44 (d of d, 1 H, J_{9-8} = 9.1 Hz, J_{9-11} = 2.2 Hz), 8.90 (s, 1 H), 9.82 (d, 1 H, J_{11-9} = 2.1 Hz), 12.47 (s, 2 H); exact mass calcd for $C_{17}H_{10}N_4O_2$ 302.0804, found 302.0804.

Bromination of Pyridodiindoles with NBS in CH_2Cl_2/TFA (Representative Procedure). 10-Bromo-7,12-dihydropyrido[3,2-*b*:5,4-*b*']diindole (13). The base **1** (0.0620 g, 0.241 mmol) was dissolved in dichloromethane (50 mL) and trifluoroacetic acid (15 mL) at 25 °C. *N*-Bromosuccinimide (0.0429 g, 0.241 mmol) was added in one portion, and the solution was stirred for 16 h. The solvent was removed under reduced pressure, and the resulting solid was taken up in water (10 mL). The aqueous solution was added to aqueous Na_2CO_3 (satd, 50 mL) and the mixture extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with brine (50 mL) and dried (Na_2CO_3). The solvent was removed in vacuo to yield a light green solid, which was purified by flash column chromatography (SiO_2, EtOAc) to afford **13** (0.0590 g, 73%): mp >300 °C; IR (KBr) 3390, 1470, 800 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 7.27 (d of t, 1 H, $J_{3-2(4)}$ = 7.3 Hz, J_{3-1} = 0.7 Hz), 7.44 (d of t, 1 H, $J_{2-1(3)}$ = 7.6 Hz, J_{2-4} = 1.1 Hz), 7.64 (m, 2 H), 7.68 (d of d, 1 H, J_{9-8} = 7.6 Hz, J_{9-11} = 1.5 Hz), 8.18 (d, 1 H, J_{4-3} = 7.6 Hz), 8.82 (s, 1 H), 9.00 (d, 1 H, J_{11-9} = 1.1 Hz), 12.06 (s, 1 H), 12.13 (s, 1 H); mass spectrum (EI; 15 eV), m/e (relative intensity) 337 (M + 2, 99), 335 (M$^+$, 100).

Anal. Calcd for $C_{17}H_{10}N_3Br{\cdot}1^1/_4H_2O$: C, 56.92; H, 3.51; N, 11.71. Found: C, 57.04; H, 3.09; N, 11.77.

3,10-Dibromo-7,12-dihydropyrido[3,2-*b*:5,4-*b*']diindole (14): see entry 4, Table IV, for stoichiometry; 96%; mp >300 °C (EtOAc); IR (KBr) 3436, 1465, 1384, 1230, 800 cm^{-1}; ^{1}H NMR (Me_2sO-d_6) δ 7.55 (d of d, 1 H, J_{2-1} = 8.4 Hz, J_{2-4} = 1.8 Hz), 7.63 (d, 1 H, J_{1-2} = 8.4 Hz), 7.65 (d, 1 H, J_{8-9} = 8.8 Hz, 7.69 (d of d, 1 H, J_{9-8} = 8.8 Hz, J_{9-11} = 1.6 Hz), 8.27 (d, 1 H, J_{4-2} = 1.8 Hz), 8.86 (s, 1 H), 8.98 (s, 1 H), 12.17 (s, 1 H), 12.34 (s, 1 H); mass spectrum (EI; 15 eV), m/e (relative intensity) 417 (49), 415 (100), 413 (51); exact mass calcd for $C_{17}H_9N_3Br_2$ 414.9143, found 414.9154.

Anal. Calcd for $C_{17}H_9N_3Br_2{\cdot}^1/_2H_2O{\cdot}^1/_2C_4H_8O_2$: C, 48.75; H, 3.01; N, 8.98. Found: C, 48.60; H, 2.78; N, 9.18.

Chlorination of 1 with NCS in CH_2Cl_2/TFA (Representative Procedure). The base **1** (0.0557 g, 0.216 mmol) was dissolved in dichloromethane (80 mL) and trifluoroacetic acid at room temperature. An excess of *N*-chlorosuccinimide (0.1561 g, 1.169 mmol) was added in one portion, and the solution was stirred for 48 h. The solvent was removed under reduced pressure, the residue was taken up in water (50 mL), and the mixture was added to aqueous Na_2CO_3 (saturated, 100 mL). The solution was extracted with EtOAc (3 × 100 mL), and the organic layers were combined, washed with brine (100 mL), and dried (Na_2CO_3). The solvent was removed under reduced pressure to yield a green-colored solid (0.0657 g), which was comprised of several products [TLC (SiO_2, EtOAc)]. Flash column chromatography (SiO_2, EtOAc) was employed to isolate the major components.

3,10-Dichloro-7,12-dihydropyrido[3,2-*b*:5,4-*b*']diindole (17): 0.021 g (30%); mp >300 °C (EtOAc); ^{1}H NMR (Me_2SO-d_6) δ 7.47 (d of d, 1 H, J_{2-1} = 8.5 Hz, $J_{2-1} \approx$ 2 Hz), 7.58 (d of d, 1 H, J_{9-8} = 8.8 Hz, $J_{9-11} \approx$ 2 Hz), 7.67 (d, 1 H, J_{8-9} = 9.3 Hz), 7.70 (d, 1 H, J_{1-2} = 9.0 Hz), 8.13 (s, 1 H), 8.86 (s, 2 H), 12.13 (s, 1 H), 12.30 (s, 1 H); mass spectrum (CI, CH_4), m/e (relative intensity) 330 (11), 328 (61), 326 (100).

Anal. Calcd for $C_{17}H_9N_3Cl_2{\cdot}^1/_2C_4H_8O_2$: C, 61.64; H, 3.54; N, 11.35. Found: C, 61.49; H, 3.13; N, 11.28.

1,10-Dichloro-7,12-dihydropyrido[3,2-*b*:5,4-*b*']diindole (18): 0.015 g (21%): mp >300 °C (EtOAc); ^{1}H NMR (Me_2SO-d_6) δ 7.28 (t, 1 H, $J_{3-2(4)}$ = 7.8 Hz), 7.52 (d, 1 H, J_{2-3} = 8.2 Hz), 7.57 (d of d, 1 H, J_{9-8} = 8.6 Hz, J_{9-11} = 1.8 Hz), 7.69 (d, 1 H, J_{8-9} = 8.5 Hz), 8.15 (d, 1 H, J_{4-3} = 7.8 Hz), 8.89 (s, 1 H), 9.32 (s, 1 H), 12.17 (s, 2 H); mass spectrum (CI, CH_4), m/e (relative intensity) 330 (11), 328 (56), 326 (100).

3,10-(7,12-Dihydropyrido[3,2-*b*:5,4-*b*']diindole)disulfonic Acid, Disodium Salt (19). The pyridodiindole **1** (0.0426 g, 0.166 mmol) was dissolved in sulfuric acid (concentrated, 3.5 mL) at room temperature. The solution was stirred vigorously for 4.5 h. The acidic medium was slowly added to water (40 mL) and the aqeuous solution adjusted to pH 7 with solid sodium bicarbonate. The water was removed under reduced pressure, and the solid which resulted was stirred in methanol (2 × 50 mL) for 1 h. The inorganic salts were filtered and the methanolic fractions combined. The methanol was removed in vacuo to yield a light yellow solid (1 g), which was observed by TLC to contain the organic acid. The solid was stirred in ethanol (3 × 30 mL), and the inorganic salts were filtered. The ethanolic layers were combined, and the solvent was removed under reduced pressure. The pale yellow solid (0.1033 g) which resulted was added to dimethyl sulfoxide (2 mL) and stirred for 1 h. The inorganic salts were filtered, and the solvent was removed by vacuum distillation to yield the disulfonate **19** (0.0608 g, 80%): mp >300 °C; IR (KBr) 3417, 1181, 1082, 1031 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 7.56 (d, 1 H, J_{1-2} = 8.4 Hz), 7.58 (d, 1 H, J_{8-9} = 8.5 Hz), 7.71 (d of d, 1 H, J_{2-1} = 8.5 Hz, J_{2-4} = 1.6 Hz), 7.86 (d of d, 1 H, J_{9-8} = 8.4 Hz, J_{9-11} = 1.4 Hz), 8.46 (s, 1 H), 8.82 (s, 1 H), 9.04 (s, 1 H), 12.18 (s, 1 H), 12.44 (s, 1 H); high-resolution mass spectrum sample did not vaporize.

Bromination of 1 with Br_2 in HOAc/NaOAc (Representative Procedure). The pyridodiindole **1** (0.46 g, 1.80 mmol) was added to anhydrous NaOAc (5.9 g, 7.20 mmol; 40 equiv), and the mixture was dissolved in glacial acetic acid (25 mL). Molecular bromine (0.324 g, 1.80 mmol) was added dropwise, and the mixture was stirred at room temperature for 24 h. The solvent was re-

moved under reduced pressure, and the residue was stirred in water (25 mL) for 1 h. The solid which resulted was filtered, rinsed with water, dried (air), and analyzed by mass spectrometry and HPLC. See Table IV for results.

Acknowledgment. This work was supported by grants from the National Institutes of Health (MH 36644 and NS 22287). We would like to thank Dr. Dennis Bennet (UWM) and Dr. Louis A. Trudell of Maccomb County Community College, Warren, MI, for their helpful suggestions and stimulating discussions. Support for this research was also provided by the graduate school (UWM), the Shaw Foundation and BRSG (NIH).

Registry No. 1, 98263-45-7; **5**, 106252-03-3; **6**, 115513-66-1; **7**, 115513-67-2; **8**, 106252-01-1; **9**, 115513-68-3; **10**, 115513-69-4; **13**, 115513-70-7; **14**, 115513-71-8; **17**, 115513-72-9; **18**, 115513-73-0; **19**, 115533-08-9.

Reaction of Sulfonimidamide Anions with Electrophiles

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Received February 2, 1988

The reaction of alkylsulfonimidamides with bases gave corresponding carbanions, which were allowed to react with carbonyl compounds to give (2-hydroxyalkyl)sulfonimidamides in good yields. When benzoic anhydride or chlorotrimethylsilane was treated with these anions, corresponding phenacylsulfonimidamides or (trimethylsilyl)methylsulfonimidamides were obtained. On the other hand, the reaction of methyl *N*-*p*-tosylsulfonimidmorpholide anion with carbonyl compounds afforded epoxides or oxetanes in good yields.

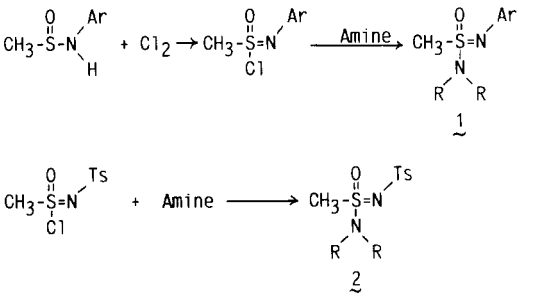
Sulfonamidamides (**1**) and *N*-*p*-tosylsulfonimidamides (**2**), derivatives of sulfonic acid, have been known since their preparation by Levchenco and co-workers in 1963, but very few reports dealing with their reactions have appeared.[1] Only one example mentions the reduction of **1** with aluminum amalgam to give sulfinamides.[2] Previously, we reported the alkylation of alkylsulfonimidamides **1b** to yield corresponding diaminooxosulfonium salts.[3] The reaction of these salts with base afforded corresponding ylides, which were treated with carbonyl compounds to give not only epoxides but also cyclopropyloxosulfonium salts.[4] This anomalous reactivity, in turn, prompted us to investigate the reactions of **1** and **2**. In this paper, we would like to report the reaction of alkylsulfonimidamide anions (**3**) and *N*-*p*-tosylsulfonimidmorpholide anion (**4**) with electrophiles.

Results and Discussion

Sulfonimidamides (**1**) were prepared by the reaction of sulfinamides, chlorine gas, and secondary amines. Compound **2** was prepared by the method described by Johnson et al.[1c] (Scheme I, Table I).

Treatment of **1a** with *n*-BuLi resulted in the formation of corresponding anion (**3a**), which was allowed to react with benzophenone in refluxing ether to give 2-hydroxysulfonimidamide (**5a**) in 62% yield (Scheme II, Table II). However, **1a** was recovered more than 70% when this reaction was carried out at 0 °C. This result showed that the reactivity of the anions **3** toward carbonyl compounds was lower than that of sulfoximide anion (**6**).[1c] We then tried the reaction of **3b** with many kinds of electrophiles. The reaction of **3b** with benzoic anhydride afforded phenacylsulfonimidmorpholine **7a** in 50.5% yield. As shown

Scheme I



Scheme II

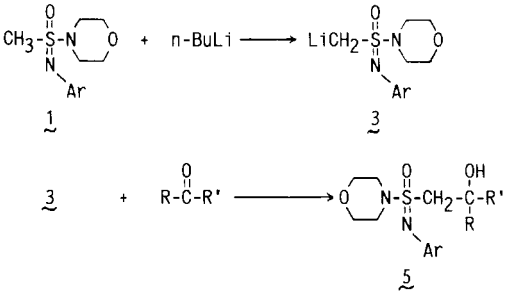


Table I. Preparation of 1 and 2

	R-N-R	Ar	yield, %
1a	morpholide	*p*-Tol	73.0
1b	morpholide	*p*-Br-C_6H_4	69.1
1c	morpholide	*p*-Cl-C_6H_4	53.7
1d	Me, Me	*p*-Cl-C_6H_4	48.7
1e	Me, Ph	*p*-Cl-C_6H_4	32.9
2	morpholide	*p*-Tosyl	92.3

Table II. Preparation of 2-Hydroxysulfonimidmorpholide (5)

	Ar		R	R′	yield, %
3a	Tol	**5a**	Ph	Ph	61.7
3b	*p*-BrC_6H_4	**5b**	H	Ph	47.8
3b	*p*-BrC_6H_4	**5c**	Ph	Ph	62.7

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