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Use of [2,3] Sigmatropic Rearrangements for the Specific Ortho-Substitution of Polycyclic Aromatic Amines. The Methylation of Naphthylamines and the Synthesis of 1*H*-Benz[*g*]indoles and 3*H*-Benz[*e*]indoles

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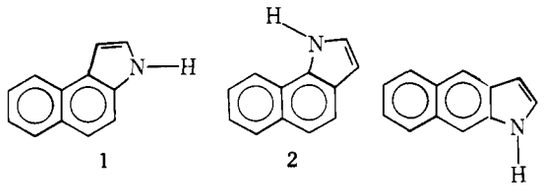
Procedures have been developed for the specific ortho-alkylation of polycyclic aromatic amines. Both α- and β-naphthylamine have been ortho-methylated by a procedure involving sequential treatment of the amine with (a) *tert*-butyl hypochlorite, (b) dimethyl sulfide, (c) sodium methoxide, and (d) Raney nickel. This procedure, which uses a [2,3] sigmatropic rearrangement of an ylide in the key ring functionalization step, gave only ortho-substitution. Replacement of the dimethyl sulfide by sulfides having a carbonyl group in the β position permitted the synthesis of 1*H*-benz[*g*]indoles and 3*H*-benz[*e*]indoles from the appropriate naphthylamine precursors.

Recently, the need for general methods for the specific ortho-substitution of polycyclic aromatic amines has been discussed in connection with oncological studies of related nonsubstituted aromatic amines.[1] Being fully aware of the need for such selective procedures for ortho-alkylation and also of the lack of good general methods for the synthesis of 1*H*-benz[*g*]indoles and 3*H*-benz[*e*]indoles, we decided to attempt to apply our general procedures for ortho-alkylation[2-6] and for the synthesis of indoles[6-9] to the polycyclic aromatic amines. We now wish to report in detail the specific ortho-substitution of α- and β-naphthylamine.

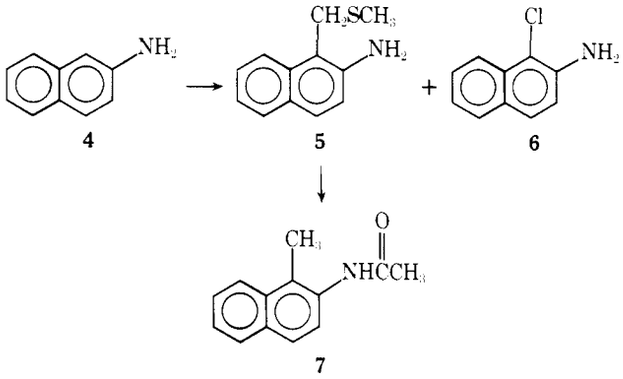
Benzindoles, although first reported in the literature in the late 19th century,[10,11] have not been extensively studied. 3*H*-Benz[*e*]indole (**1**) was first described in 1886,[10] while 1*H*-benz[*g*]indole (**2**) was reported the following year.[11] Both were prepared through application of the Fischer indole synthesis.[12] Subsequently, a variety of methods appeared in the literature for the preparation of **1** and **2** and for derivatives of these two systems.[13] It is interesting to note at this point that sound chemical evidence for the structure of **1** has never been provided. Instead, the structure of **1** was postulated on the basis of its nonidentity with 1*H*-benz[*f*]indole (**3**). As part



1 **2** **3**

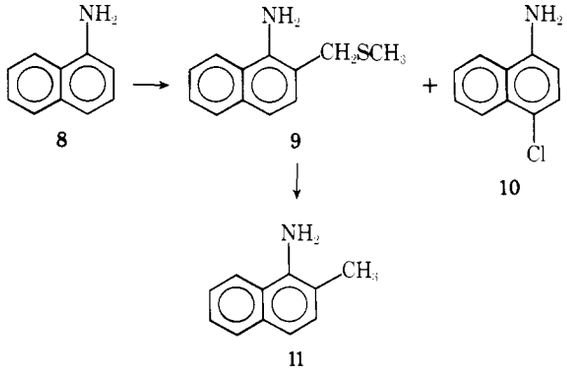
of the present study, we have provided what we believe to be a definitive structure proof of the 3*H*-benz[*e*]indole nucleus.

We first examined the simple ortho-alkylation of 2-aminonaphthalene (**4**) according to our standard process. In a sequential series of reactions, 1 equiv of *tert*-butyl hypochlorite, 1 equiv of dimethyl sulfide, and 1.5 equiv of sodium methoxide were added to 1 equiv of **4** at −78 °C. Workup gave a 95% yield of a 3:1 mixture of **5** and **6**. Separation of the mixture followed by Raney nickel desulfurization of **5** and



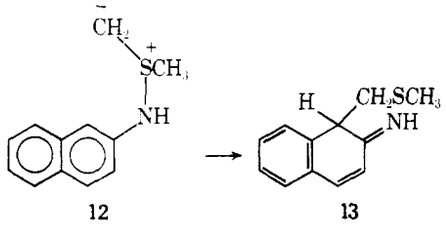
4 **5** **6** **7**

acetylation with acetyl chloride gave a 70% overall yield of the recrystallized acetamide **7**. A similar study was carried out with α-naphthylamine (**8**) as the starting material. Under our standard reaction conditions **8** gave 40% yields of **9** and **10**. Raney nickel desulfurization of **9** gave a 90% yield of **11**. Overall, the preparation of **7** and **11** illustrate the utility of our general process for ortho-alkylation of polycyclic aromatic

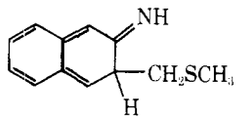


8 **9** **10** **11**

amines. Since the crucial step in the process involves the [2,3] sigmatropic rearrangement of ylides derived from azasulfonium salts such as **12**, only ortho-substitution via dienone imines such as **13** was possible. Hydrogen transfer accompanied by rearomatization then produces products such as **5**. The sigmatropic nature of the aromatic substitution step results in little, if any, charge buildup on the aromatic nucleus. Thus, polar substituents on the ring should have little effect on such substitution reactions. It is interesting to note that the rearrangement of **12** was highly specific in that only the 1 position was attacked. This was probably due to the loss of aromaticity which would result from attack at the 3 position, since initial substitution at that point would produce **14**, in which the aromatic resonance energy of both rings would be temporarily lost.

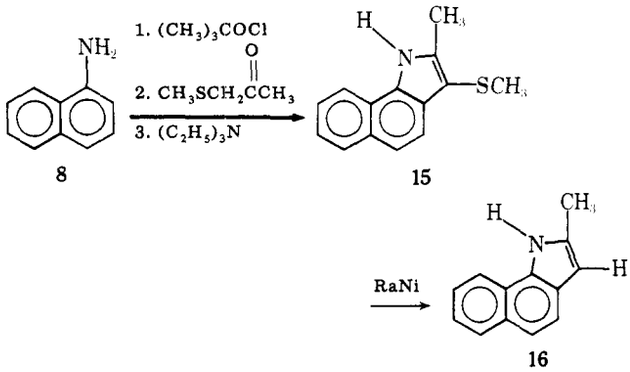


12 **13**



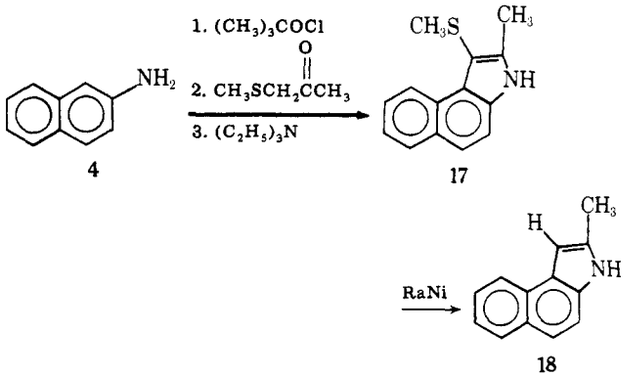
14

In order to explore the utility of our indole synthesis with polycyclic aromatic amines, the preparation of 1*H*-benz[*g*]-indoles and 3*H*-benz[*e*]indoles was attempted via replacement of the dimethyl sulfide from the procedure described above with an appropriate β-keto sulfide. Treatment of **8** with 1 equiv of *tert*-butyl hypochlorite followed by 1 equiv of methylthio-2-propanone and then by triethylamine gave a 65% yield of **15**. Raney nickel desulfurization of **15** gave a 90% yield of **16**. In a similar fashion, β-naphthylamine was converted into 1-methylthio-2-methyl-3*H*-benz[*e*]indole (**17**) in 73% yield. Raney nickel desulfurization of **17** gave **18** in 88% yield.

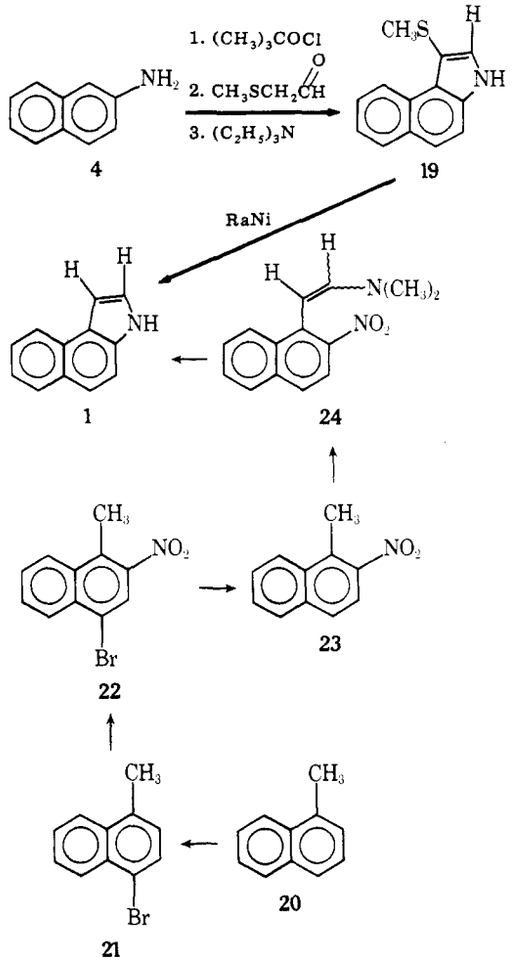


8 **15** **16**

While spectroscopic data indicated that **4** gave exclusively the 3*H*-benz[*e*]indole system, it was felt that a sound chemical proof of structure was merited. Toward this end, **4** was converted into **19** and, subsequently, into **1** by our general procedure. An authentic sample of **1** was prepared by an alternate and what we believe is an unequivocal route. As shown below, the alternate synthesis is based on the elegant Leimgrüber indole synthesis.[13j] Thus, 1-methylnaphthalene (**20**) was brominated to give a 95% yield of **21**. Nitration of **21** with nitric acid–sulfuric acid mixture gave 77% of **22**. Cuprous oxide reduction of **22** gave a 57% yield of **23**. Reaction of **23** with dimethylformamide diethyl acetal gave **24**, which was converted into **1** on reduction over palladium on carbon. The yield of **1** from **23** was 24% and the overall yield based on **20** was 10%.



4 **17** **18**



4 **19** **1** **24** **23** **22** **20** **21**

The samples of **1** prepared by the two different routes were identical in all respects.

In summary, we have demonstrated that our general processes for the ortho-alkylation of aromatic amines and for the preparation of indole derivatives can be readily extrapolated to polycyclic aromatic amines.

Experimental Section[14]

Caution! The aminonaphthalenes, 4 and 8, are known carcinogens. As such, they should only be handled under proper working conditions and by experienced personnel.

1-Methylthiomethyl-2-aminonaphthalene (5). To a stirred solution of 2.86 g (0.02 mol) of **4** in 75 mL of tetrahydrofuran, which was cooled to ca. −70 °C, was added dropwise 2.20 g (0.02 mol) of *tert*-butyl hypochlorite with vigorous stirring under a nitrogen atmosphere. The reaction mixture was stirred for 5 min, 1.5 mL (0.02 mol) of di-

methyl sulfide was added, and the reaction mixture was stirred for an additional 2 h at −70 °C. A solution of sodium methoxide (1.60 g, 0.03 mol) in 10 mL of methanol was then added dropwise and the reaction mixture was stirred until it reached room temperature. The inorganic salts were removed by filtration and the tetrahydrofuran was removed under reduced pressure. The residue was dissolved in 50 mL of ether and this solution was washed with three 30-mL portions of water. The ether layer was dried over anhydrous magnesium sulfate and filtered, and the filtrate was concentrated under reduced pressure to give a dark red oil in essentially quantitative yield. Analysis of this oil by high-pressure liquid chromatography showed it to contain 5% of **4**, 24% of 1-chloro-2-aminonaphthalene (**6**), and 71% of 1-methylthiomethyl-2-aminonaphthalene (**5**). These components were separated by preparative HPLC using a ¼ in. × 2 ft μ-poracil column with chloroform–petroleum ether as eluent. The 1-chloro-2-aminonaphthalene (**6**) had spectral and physical properties identical with those reported in the literature for this compound, mp 59.5–60.5 °C (lit.[15] mp 58–59 °C).

The 1-methylthiomethyl-2-aminonaphthalene (**5**) which was separated crystallized on standing: mp 41–42 °C; IR (neat) 2.91, 2.98, 6.14, 6.60, 6.96, 12.3, 12.5 μm; NMR ($CDCl_3$) δ 2.00 (3 H, s), 4.02 (4 H, br s), 6.80 (1 H, d), 8.0–7.0 (5 H, m).

Anal. Calcd for $C_{12}H_{13}NS$: C, 70.89; H, 6.44; N, 6.89. Found: C, 70.78; H, 6.37; N, 6.86.

1-Methyl-2-aminonaphthaleneacetamide (7). To a stirred solution of 0.47 g of **5** in 50 mL of methanol was added ~9 g of freshly prepared W-2 Raney nickel. The reaction mixture was stirred for 1 h at room temperature and the organic solution was decanted. The Raney nickel residue was washed with two 50-mL portions of methanol. The methanolic solutions were combined and filtered through Celite, and the filtrate was concentrated at reduced pressure. The residue was dissolved in chloroform, washed with saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and filtered. Concentration of the filtrate under reduced pressure gave a red oil, which was chromatographed on silica gel (hexane–ether eluent) to yield the desired 1-methyl-2-aminonaphthalene: IR (neat) 2.89, 2.96, 6.16, 6.64, 7.22, 12.44, 13.5 μm; NMR ($CDCl_3$) δ 2.30 (3 H, s), 3.65 (2 H, br s), 6.85 (1 H, d), 8.0–7.0 (5 H, m). This material was allowed to react with acetyl chloride in pyridine to yield 0.32 g (70%) of **7** after recrystallization from ethanol, mp 188–189 °C (lit.[16] mp 189 °C).

2-Methylthiomethyl-1-aminonaphthalene (9). The procedure used in the synthesis of **9** was identical with that described above for the preparation of **5**. A mixture, which contained a 40% yield of 1-chloro-4-aminonaphthalene (**10**) and a 40% yield of 2-methylthiomethyl-1-aminonaphthalene (**9**), was obtained. The structure of **10** was established through the identity of its spectral properties and physical constants with those in the literature, mp 93–95 °C (lit.[17] mp 95–97 °C). The 2-methylthiomethyl-1-aminonaphthalene (**9**) had the following properties: mp 40–42 °C; IR (neat) 2.88, 2.95, 6.16, 6.62, 6.92, 7.20 μm; NMR ($CDCl_3$) δ 1.95 (3 H, s), 3.80 (2 H, s), 4.41 (2 H, s), 7.9–7.1 (6 H, m).

Anal. Calcd for $C_{12}H_{13}NS$: C, 70.89; H, 6.44; N, 6.89. Found: C, 70.78; H, 6.55; N, 6.70.

1-Amino-2-methylnaphthalene (11). To a stirred solution of 0.20 g of **9** in 50 mL of methanol was added ~6 g of W-2 Raney nickel and the reaction mixture was stirred at room temperature for 2 h. The methanol solution was decanted and the Raney nickel residue was washed twice with 50-mL portions of methanol. The combined methanol solution was filtered through Celite, and the solvent was removed under reduced pressure. The residue was dissolved in methylene chloride, washed with three 30-mL portions of water, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give 0.14 g (90%) of 1-amino-2-methylnaphthalene (**11**), which was shown to be pure by HPLC analysis: IR (neat) 2.88, 2.95, 6.16, 6,60, 7.12, 7.23, 12.60, 12.99, 13.52 μm; NMR ($CDCl_3$) δ 2.17 (3 H, s), 3.80 (2 H, br s), 7.9–7.0 (6 H, m). A hydrochloride was prepared, mp 227–230 °C (lit.[18] mp 228–231 °C).

1-Methylthio-2-methyl-3*H*-benz[*e*]indole (17). To a stirred solution of 3.75 g (26 mmol) of 2-aminonaphthalene (**4**) in 75 mL of tetrahydrofuran at ca. −70 °C was added dropwise 2.83 g (26 mmol) of *tert*-butyl hypochlorite under a nitrogen atmosphere. The reaction mixture was stirred at −70 °C for 5 min and 2.73 g (26 mmol) of methylthio-2-propanone[7,9] in 10 mL of tetrahydrofuran was added dropwise. A voluminous white precipitate formed shortly after this addition. The reaction mixture was stirred for 2 h at ca. −70 °C, followed by the dropwise addition of 5 mL of triethylamine. The cooling bath was removed and the reaction mixture was stirred until it reached room temperature. Distilled water (10 mL) was added and the organic layer was separated and concentrated under reduced pressure. The residue was dissolved in 50 mL of ether and the ethereal solution was washed with three 30-mL portions of 1 N hydrochloric acid and one 30-mL portion of distilled water. The ether layer was dried over anhydrous magnesium sulfate and filtered, and the filtrate was concentrated under reduced pressure to give crude **17**. Chromatography on silica gel (benzene eluent) gave 4.5 g (76%) of 1-methylthio-2-methyl-3*H*-benz[*e*]indole (**17**), mp 112–113 °C. Recrystallization from hexane gave an analytical sample: mp 112.0–112.5 °C; IR (KBr) 2.90, 7.29, 7.52, 8.30, 10.35, 12.35, 13.36, 14.42 μm; NMR ($CDCl_3$) δ 2.25 (3 H, s), 2.37 (3 H, s), 7.0–8.0 (6 H, m), 9.60 (1 H, d).

Anal. Calcd for $C_{14}H_{13}NS$: C, 73.97; H, 5.76; N, 6.16. Found: C, 73.96; H, 5.78; N, 6.21.

2-Methyl-3*H*-benz[*e*]indole (18). To a vigorously stirred solution of 2.0 g (8.8 mmol) of **17** in 100 mL of ethanol was added ~20 g of W-2 Raney nickel. The slurry was stirred for 1 h and the ethanolic solution was decanted. The Raney nickel residue was washed with two 100-mL portions of ethanol and the solutions were combined and filtered through Celite. The solvent was removed under reduced pressure, the residue was dissolved in 50 mL of dichloromethane and washed with distilled water, and the organic solution was dried over anhydrous magnesium sulfate. After filtration, the filtrate was concentrated under reduced pressure and the residue was chromatographed on silica gel (benzene eluent) to give 1.20 g of a light yellow oil. Molecular distillation of the material gave 1.10 g (88%) of pure 2-methyl-3*H*-benz[*e*]indole: IR (neat) 2.93, 3.28, 6.50, 7.35, 12.50, 13.10, 13.45 μm; NMR ($CDCl_3$) δ 2.40 (3 H, s), 6.75 (1 H, m), 8.3–7.1 (6 H, m).

Anal. Calcd for $C_{13}H_{11}N$: C, 86.15; H, 6.12; N, 7.73. Found: C, 85.90; H, 6.08; N, 7.66.

3-Methylthio-2-methyl-1*H*-benz[*g*]indole (15). A procedure identical with that described above for the preparation of **17** was used to convert **8** into **15** (65% yield): mp 117–118 °C; IR (KBr) 2.93, 7.23, 12.85, 13.85, 18.40 μm; NMR ($CDCl_3$) δ 2.28 (3 H, s), 2.55 (3 H, s), 8.05–7.15 (6 H, m), 8.55 (1 H, br s).

Anal. Calcd for $C_{14}H_{13}NS$: C, 73.97; H, 5.76; N, 6.16. Found: C, 73.78; H, 5.78; N, 6.21.

2-Methyl-1*H*-benz[*g*]indole (16). The procedure used for the preparation of **16** was identical with that described above for the synthesis of **18**. In this manner **16** was prepared in 90% yield: mp 134–135 °C (lit.[11,13e] mp 132 °C, 132.5–136.0 °C); IR (KBr) 2.94, 6.49, 7.22, 12.49, 13.43, 14.67, 19.20, 20.10 μm; NMR ($CDCl_3$) δ 2.52 (3 H, s), 6.38 (1 H, br s), 8.15–7.20 (6 H, m), 8.6 (1 H, br s).

Anal. Calcd for $C_{13}H_{11}N$: C, 86.15; H, 6.12; N, 7.73. Found: C, 85.92; H, 6.14; N, 7.76.

1-Methylthio-3*H*-benz[*e*]indole (19) and 3*H*-Benz[*e*]indole (1). To a stirred solution of 2.86 g (20 mmol) of **4** in 75 mL of tetrahydrofuran at ca. −70 °C was added dropwise 2.20 g (20 mmol) of *tert*-butyl hypochlorite under nitrogen. After stirring for 5 min, a solution of 1.80 g (20 mmol) of methylthioacetaldehyde[7,9] in 10 mL of tetrahydrofuran was added dropwise and the reaction mixture was stirred for 4 h at ca. −70 °C. Triethylamine (5 mL) was added and the reaction mixture was stirred and allowed to warm to room temperature. When the reaction mixture reached room temperature it was filtered and the filtrate was concentrated under reduced pressure to yield a dark oil, which was dissolved in 100 mL of ether, washed with three 30-mL portions of water, and dried over anhydrous magnesium sulfate. After filtration, the filtrate was concentrated under reduced pressure and the residue was shown to contain a 2:1 mixture of 1-chloro-2-aminonaphthalene and 1-methylthio-3*H*-benz[*e*]indole (**19**) along with several minor components by HPLC analysis. Purification by chromatography on silica gel (ether–hexane eluent) gave 0.37 g of **19** as a red oil: NMR ($CDCl_3$) δ 2.44 (3 H, s), 7.92–7.20 (6 H, m), 8.58 (1 H, br s), 9.23 (1 H, d).

This material was dissolved in 50 mL of methanol and stirred with ~9 g of W-2 Raney nickel for 3 h at room temperature. The methanol solution was decanted and the Raney nickel residue was washed with two 50-mL portions of methanol. The combined methanolic solution was filtered through Celite, and the filtrate was concentrated under reduced pressure. The residue was dissolved in 50 mL of methylene chloride and the solution was washed with three 30-mL portions of water, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under reduced pressure to yield 0.24 g (8% based on **4**) of 3*H*-benz[*e*]indole (**1**) as a yellow oil: IR (neat) 2.93, 7.37, 12.60, 13.50, and 13.90 μm; NMR ($CDCl_3$) δ 8.5–6.9 (9 H, m).

4-Bromo-1-methylnaphthalene (21). This material was prepared from 1-methylnaphthalene (**20**) according to the procedure of Topsom and Vaughan[19] in 95% yield: bp 170–171 °C (20 mm); n^{25}_D 1.6500 [lit.[19] bp 170–171 °C (20 mm)].

4-Bromo-1-methyl-2-nitronaphthalene (22). The procedure of Veselý and co-workers[20] was used to convert **21** into **22** in 77% yield: mp 119.5–120.5 °C (lit.[19,20] mp 122 °C).

1-Methyl-2-nitronaphthalene (23). This compound was prepared by reduction of **22** according to the literature procedure[19] to give 57% of **23**: mp 59–60 °C (lit.[19] mp 56 °C); IR (KBr) 6.59, 7.40, 12.30, 12.56, 13.30 μm; NMR ($CDCl_3$) δ 3.77 (3 H, s), 8.4–7.5 (6 H, m).

1-(*N,N*-Dimethylamino)-2-(2-nitro-1-naphthyl)ethene (24) and 3*H*-Benz[*e*]indole (1). A solution of 2.60 g (17.7 mmol) of dimethylformamide diethyl acetal and 3.30 g (17.6 mmol) of **23** in 10 mL of dry dimethylformamide was heated to 155 °C for 3 h. The reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure to yield crude **24** as a dark red oil: IR (neat) 6.14, 6.60, 7.30, 9.14, 12.50, 13.25 μm; NMR ($CDCl_3$) δ 2.80 (6 H, s), 5.66 (1 H, d, J = 13.7 Hz), 6.40 (1 H, d, J = 13.7 Hz). This material was used in the following step without additional purification.

The material obtained above was dissolved in 50 mL of benzene in a Parr hydrogenation vessel and 0.25 g of 5% palladium on carbon was added. This material was hydrogenated at 40 psi hydrogen pressure until the solution turned to a clear yellow. The reaction mixture was filtered through Celite and the filtrate was concentrated under reduced pressure. The residue was chromatographed on silica gel (ether–hexane eluent) to yield 0.70 g (24% based on 1-methyl-2-nitronaphthalene) of 3*H*-benz[*e*]indole (1). This material was identical in all respects with that described above.

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Registry No.—1, 232-84-8; **4**, 91-59-8; **5**, 63017-82-3; **8**, 134-32-7; **9**, 34774-85-1; **11**, 2246-44-8; **15**, 63017-83-4; **16**, 18505-87-8; **17**, 63017-84-5; **18**, 57582-31-7; **19**, 63017-85-6; **20**, 90-12-0; **21**, 6627-78-7; **22**, 63017-86-7; **23**, 63017-87-8; **24**, 63017-88-9; 1-methyl-2-aminonaphthalene, 771-13-1; methylthio-2-propanone, 14109-72-9; methylthioacetaldehyde, 23328-62-3; dimethylformamide diethyl acetal, 1188-33-6.

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Hydroboration of Alkenes and Alkynes by 1,3,2-Dithiaborolane

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Treatment with diethyl ether–trifluoroborane or trichloroborane liberates 1,3,2-dithiaborolane (3) from its complex with trimethylamine. At 50 °C in benzene, hydroboration by 1,3,2-dithiaborolane efficiently converts a representative group of alkenes and alkynes into alkyl- and alkenyl-1,3,2-dithiaborolanes. Hydrolysis of these products yields the corresponding boronic acids.

From studies of boronic acids and their derivatives have come several important developments. Meriting special attention is the observation that certain derivatives of benzeneboronic acid accumulate in tumors of the brain.[1] Since ^{10}B has an unusually large cross section for the capture of thermal neutrons and since subsequent nuclear fission of $^{11}_{5}B$ releases locally lethal amounts of energy, neutron irradiation can be used to destroy the cells of tumors selectively.[2] The powerful, reversible inhibition of α-chymotrypsin and subtilisin by 2-phenylethaneboronic acid and benzeneboronic acid has given boronic acids a role to play in the study of specific inhibitors of enzymes.[3] Finally, boronic acids are useful intermediates in syntheses: for example, terminal alkynes can be converted into *trans*-vinyl iodides and *cis*-vinyl bromides;[4a] oxidation of boronic acids $RB(OH)_2$ with ammoniacal silver oxide gives simple coupled products R–R;[4b] a cross-coupling reaction mediated by boronate complexes derived from boronic esters and vinyllithium reagents can be used to prepare substituted olefins;[4c] and the reactions of carbonyl compounds with lithium bis(ethylenedioxyboryl)methide and then with hydrogen peroxide yield the homologous aldehydes.[4d]

An old, general method for preparing boronic acids and esters employs the reaction of appropriate organometallic compounds with esters of boric acid.[5] Redistribution reactions of trialkylboranes[6] or tetraalkylstannanes[7] with trichloroborane and redistribution reactions of trialkylboranes with esters of boric acid[8] produce derivatives of boronic acids, but frequently more efficient is the direct hydroboration of alk-