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Generation and Reactions of 3-Lithio-1-(phenylsulfonyl)indole

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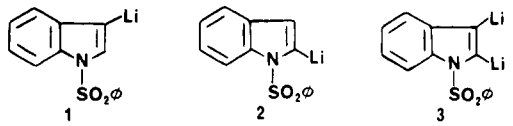
Treatment of 1-(phenylsulfonyl)-3-iodoindole (6) with 2 equiv of *tert*-butyllithium (−100 °C THF) generates essentially quantitatively 3-lithio-1-(phenylsulfonyl)indole (1). Quenching 1 with various electrophiles gives 3-substituted indoles in good yield. Upon warming to room temperature, 1 cleanly rearranges to the more stable 2-lithio-1-(phenylsulfonyl)indole (2). An alternative procedure for the generation of 2 from 1-(phenylsulfonyl)indole (8) with lithium diisopropylamide (LDA) and simple, high yield procedures for the N-sulfonation and N-acylation of indoles are also described. This new indole lithiation methodology provides a synthetic equivalency for 2,3-dilithio-1-(phenylsulfonyl)indole (3) and should find use in indole synthesis.

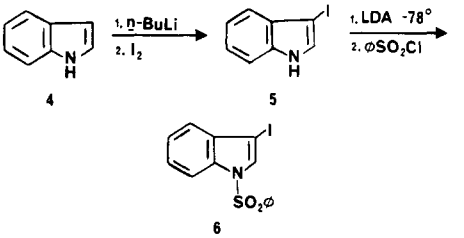
Nitrogen-protected 2-lithioindoles have been widely used in synthesis since the pioneering work of Sundberg and Russell,[1] although the regioselective 2-lithiation of 1-methylindole was described 20 years earlier[2] and several groups observed similar lithiation of N-protected indoles prior to Sundberg's detailed study.[3] In particular, the phenylsulfonyl protecting group has been extensively used in this regard.[1,4]

We now report the generation of the previously unknown 3-lithio-1-(phenylsulfonyl)indole (1) and an attractive alternative procedure for the regioselective generation of 2-lithio-1-(phenylsulfonyl)indole (2), using lithium diisopropylamide (LDA), which avoids the use of the extremely reactive *tert*-butyllithium and which provides reaction products of somewhat greater purity.[5] Moreover, when applied in sequence this methodology should afford a potentially useful synthetic equivalency for 2,3-dilithio-1-(phenylsulfonyl)indole (3).



1 2 3

Scheme I



4 5 6

This study was initiated by a need to amplify the inherent nucleophilic character of the indole 3-position in the context of a natural product synthesis. In particular, we required an N-protected indole with a highly electron-rich C-3 carbon center, and thus the familiar indole nitrogen Grignard reagents,[6] which unfortunately give competitive N- and C-3-substituted products, were unsuitable. Our present study of the generation and reactions of 3-lithio-1-(phenylsulfonyl)indole (1) now provides a species complementary to the 2-lithio analogue 2. We find 1 to be inherently more reactive and less stable than its isomeric counterpart.

Results and Discussion

Synthesis of 1-(Phenylsulfonyl)indoles. Our target molecule for the generation of 3-lithio-1-(phenylsulfonyl)indole (1) was 1-(phenylsulfonyl)-3-iodoindole (6), whose preparation is shown in Scheme I. Although 3-iodoindole (5) is well-known,[7] its syntheses are inefficient and product isolation can be difficult due to its instability.

(1) Sundberg, R. J.; Russell, H. F. *J. Org. Chem.* **1973**, *38*, 3324.
(2) Shirley, D. A.; Roussel, P. A. *J. Am. Chem. Soc.* **1953**, *75*, 375.
(3) See the literature cited in ref 1.
(4) (a) Sundberg, R. J.; Smith, F. X. *J. Org. Chem.* **1975**, *40*, 2613. (b) Taylor, D. A.; Baradarani, M. M.; Martinez, S. J.; Joule, J. A. *J. Chem. Res., Synop.* **1979**, 387. (c) Sundberg, R. J.; Broome, R.; Walters, C. P.; Schnur, D. *J. Heterocycl. Chem.* **1981**, *18*, 807. (d) Sundberg, R. J.; Parton, R. L. *J. Org. Chem.* **1976**, *41*, 163. (e) Caixach, J.; Capell, R.; Galvez, C.; Gonzalez, A.; Roca, N. *J. Heterocycl. Chem.* **1979**, *16*, 1631. (f) Bergman, J.; Eklund, N. *Tetrahedron* **1980**, *36*, 1439. (g) Kano, S.; Sugino, E.; Hibino, S. *J. Chem. Soc., Chem. Commun.* **1980**, 1241. (h) Sundberg, R. J.; Bloom, J. D. *J. Org. Chem.* **1980**, *45*, 3382.
(5) Sundberg has recently reported the dilithiation of 1-(phenylsulfonyl)indole (8) with 2 equiv of *tert*-butyllithium.[4c] We have found that minor side products result from some dilithiation of 8 via Sundberg's original method[1] (1.2 equiv of *tert*-butyllithium); these problems are not encountered when LDA is used.
(6) Heacock, R. A.; Kasparek, S. *Adv. Heterocycl. Chem.* **1969**, *10*, 43.
(7) (a) Franzen, V. *Chem. Ber.* **1954**, *87*, 1148. (b) Terent'ev, A. P.; Belen'kii, L. I.; Yanovskaya, L. A. *Zh. Obshch. Khim.* **1954**, *24*, 1265. (c) Saunders, B. C.; Stark, B. P. *Tetrahedron* **1958**, *4*, 169. (d) Arnold, R. D.; Nutter, W. M.; Stepp, W. L. *J. Org. Chem.* **1959**, *24*, 117. (e) Ermolenko, M. S.; Budylin, V. A.; Kost, A. N. *Khim. Geterotsikl. Soedin.* **1978**, *7*, 933.

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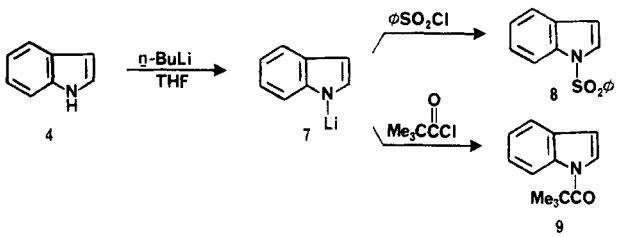
Table I. Reaction of 1, 2, 7, and 12 with Electrophiles

lithioindole	electrophile	product[a]	E	mp, °C	yield, %[b]
1	CH_3I	10a	CH_3	117-118.5[c,d]	62
1	$ClCO_2Et$	10b	CO_2Et	118.5-119.5[e]	51
1	PhCHO	10c	CHOHPh	45.5-47.5[f]	89
1	$(CH_3)_3SiCl$	10d	$(CH_3)_3Si$	105-105.5[f]	76
1	$(PhS)_2$	10e	PhS	68-68.5[e]	84
1	PhCOCl	10f	PhCO	109.5-111[e]	76
1	$HCON(CH_3)_2$	10g	CHO	158-158.5[g]	71
2	CH_3I	11a	CH_3	37-38[f]	85
2	$(PhS)_2$	11b	PhS	118.5-119[e]	75
2	$ClCO_2Et$	11c	CO_2Et	89[h]	75
2	$HCON(CH_3)_2$	11d	CHO	111-111.5[e]	50
2	CH_3CHO	11e	CH_3CHOH	101-102[f]	93
2	14	15[i]		174-175[j]	47
7	$PhSO_2Cl$	8		76-76.5[k]	91
7	Me_3CCOCl	9		65-66[l,m]	92
12	I_2	13		166-167[f]	98

[a] All new compounds gave excellent (±0.08%) elemental analyses (C, H, N, S, I) and spectral (IR, ^1H- and ^{13}C-NMR) data consistent with their assigned structures. [b] The yield refers to isolated and purified (crystallized or flash chromatographed) product. [c] From dichloromethane-hexane. [d] Lit.[16] mp 118-120.5 °C. [e] From ether-hexane. [f] Flash chromatography gave analytically pure material. [g] From dichloromethane-ether-hexane. [h] Lit.[1] mp 89-91 °C. [i] The elemental analysis was slightly off: C, -0.29%; H, +0.36%; N, -0.07%; S, -0.03%. [j] From methanol. [k] Lit.[1] mp 77.5-79 °C. [l] From hexane. [m] Lit.[9d] mp 63-64 °C.

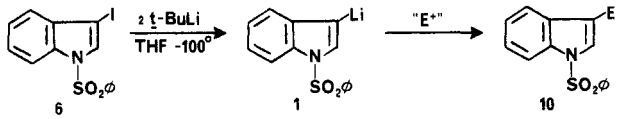
Scheme II



Therefore, we developed a simple alternative synthesis of **5**. Treating indole (**4**) with *n*-butyllithium in THF followed by the addition of iodine at −78 °C presumably generates *N*-iodoindole, which rearranges during workup to afford the more stable 3-iodoindole (**5**) in nearly quantitative yield. This compound rapidly decomposes at room temperature and, therefore, is immediately converted to **6** with LDA (THF, −78 °C) followed by treatment with benzenesulfonyl chloride. The overall yield of **6** prepared in this fashion is 66%. However, when the reaction sequence is repeated on a 10–20-g scale, the instability of isolated 3-iodoindole (**5**) apparently results in lower yields of **6**. Therefore, we have developed an efficient one-pot synthesis of **6** from **4** that can be conveniently run on a larger scale. This method employs a low-temperature-controlled inverse-addition apparatus (Figure 1) that we previously had designed for more efficient 3,4-pyridyne generation-trapping experiments.[8] With this apparatus the overall purified yield of **6** from **4** is 88%.

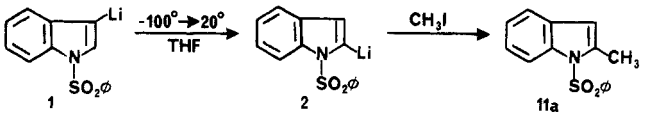
In the course of this work we have found that *n*-butyllithium/THF efficiently generates 1-lithioindole (**7**) and constitutes a very convenient method for the N-benzenesulfonation and N-acylation of indole, which avoids using Me_2SO and HMPA.[9] For example, 1-(phenylsulfonyl)-indole (**8**) and 1-(trimethylacetyl)indole (**9**) can be synthesized in high yield with this procedure as illustrated in Scheme II.

Generation of Lithioindoles. Treating **6** with 2 equiv[10] of *tert*-butyllithium (THF, −100 °C) results in the immediate formation of a light yellow color due to **1**. After 5 min this solution is treated with various electrophiles to give the products (**10**) shown in Table I. Deuterium oxide

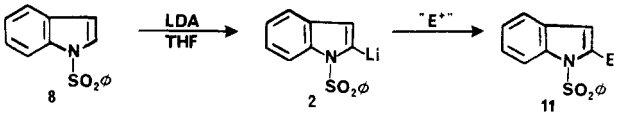


quenching affords an essentially quantitative yield of 1-(phenylsulfonyl)-3-deuterioindole. Mass spectrometry shows 96% deuterium incorporation at C-3, consistent with the disappearance of the singlet (6.50 ppm) in the ^1H NMR spectrum of **8**. The corresponding ^{13}C NMR signal (109.1 ppm) collapses to a weakly discernible triplet.

When **1** is allowed to warm to room temperature over 2 h with or without a catalytic amount of **8**, complete rearrangement to the thermodynamically more stable 2-lithio species **2** results, as evidenced by the isolation of 1-(phenylsulfonyl)-2-methylindole (**11a**) after methyl iodide quenching. No detectable amount of the isomeric 1-(phenylsulfonyl)-3-methylindole (**10a**) is obtained.



In the course of this study we have independently observed[11] that the regioselective 2-lithiation of **8** to give **2** can be achieved with LDA at low temperatures. Quenching this anion with various electrophiles gives the products (**11**) reported in Table I. We find that this



(8) Our earlier paper describing the lithiation of halopyridines (Gribble, G. W.; Saulnier, M. G. *Tetrahedron Lett.* **1980**, 4137) briefly noted the generation-trapping of 3,4-pyridyne using conventional procedures. We have since found that employment of the low-temperature-controlled inverse-addition apparatus in this regard completely avoids the usual production of dark polymeric material (a typical phenomenon with benzyne reactions) and we expect to report this in due course.

(9) (a) Gribble, G. W.; Reilly, L. W. Jr.; Johnson, J. L. *Org. Prep. Proc. Int.* **1977**, *9*, 271 and references cited therein. (b) Reference 4h. (c) Reference 1. (d) Illi, V. O. *Synthesis* **1979**, 387. (e) Kikugawa, Y. *Synthesis* **1981**, 460.

(10) (a) Neumann, H.; Seebach, D. *Tetrahedron Lett.* **1976**, 4839. (b) Neumann, H.; Seebach, D. *Chem. Ber.* **1974**, *107*, 847. (c) Corey, E. J.; Beames, D. J. *J. Am. Chem. Soc.* **1972**, *94*, 7210.

(11) (a) Kano, S.; Sugino, E.; Hibino, S. *J. Chem. Soc., Chem. Commun.* **1980**, 1241. (b) Kano, S.; Sugino, E.; Shibuya, S.; Hibino, S. *J. Org. Chem.* **1981**, *46*, 2979.

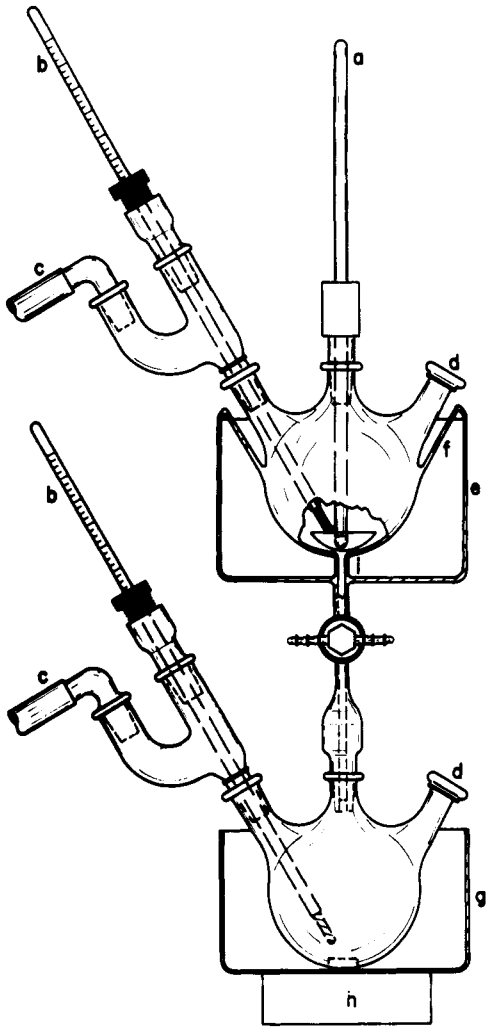
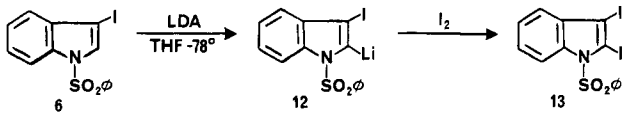


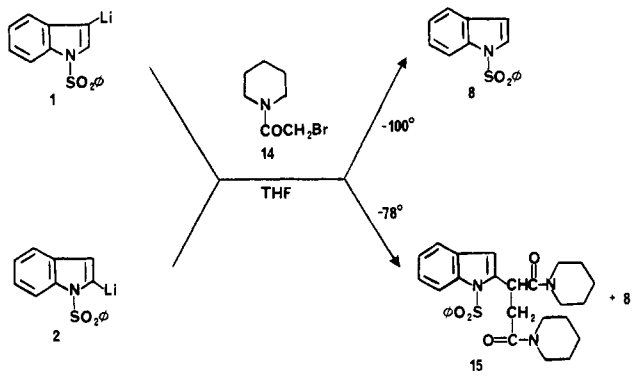
Figure 1. This inverse-addition apparatus is used to prepare air-sensitive intermediates at low temperatures in the top reaction flask (permanently attached to bath e by glass rods f). The solution of intermediate can then be added through orifice i, at a rate controlled by the Teflon stopcock, to the contents of the lower reaction flask cooled (or heated) in bath g. The flasks are equipped with thermometers (b), inert gas inlets (c), rubber septa (d), and mechanical (a) and magnetic (h) stirrers. That part of the stem connecting the top bath with the stopcock can be cooled by wrapping it with copper wire leading back into the top cooling (dry ice/acetone or liquid nitrogen) bath.

method affords cleaner reaction products of comparable or somewhat greater yield than obtained via Sundberg's procedure.[1] One clear advantage of using LDA over *tert*-butyllithium to lithiate 1-(phenylsulfonyl)indoles is that the former base is tolerated by more functional groups than is the latter. Indeed, we can lithiate **6** extremely efficiently with LDA (THF, −78 °C) to give 1-(phenylsulfonyl)-2-lithio-3-iodoindole (**12**). After the addition of iodine we obtain 1-(phenylsulfonyl)-2,3-diiodoindole (**13**) in 98% purified yield.



Thus, when applied in sequence, this new indole lithiation methodology provides a synthetic equivalency for the potentially useful 1-(phenylsulfonyl)-2,3-dilithioindole (**3**).

A useful comparison of the relative basicity vs. nucleophilicity of **1** and **2** is demonstrated in their reaction with 1-(α-bromoacetyl)piperidine (**14**).[12] Reaction with the less basic **2** proceeds by bromide displacement to generate the alkylated product. However, this rapidly undergoes deprotonation by remaining **2**, followed by further reaction with **14**, to give bisamide **15** (47%) and 1-(phenylsulfonyl)indole (**8**; 47%). The presumably more basic and highly reactive **1** predominantly enolizes **14** to give a large proportion of **8**. Indeed, the major reaction pathway of **1** with *n*-alkyl halides (e.g., ethyl bromide, ethyl iodide, 1-bromo-4-chlorobutane) is elimination, giving essentially only **8**.



This lithiation chemistry should find use in indole synthesis and we are currently pursuing this avenue of research. For example, we are exploring the possibility that **13** might serve as a precursor to the elusive 2,3-indolyne.[13]

Experimental Section

Melting points were determined with a Mel-Temp Laboratory Devices apparatus and are uncorrected. Elemental analyses were performed by Atlantic Microlabs, Atlanta, GA. Infrared spectra were recorded on a Perkin-Elmer 599 instrument. ^{1}H NMR spectra were obtained with a Hitachi Perkin-Elmer R-24 spectrometer and ^{13}C NMR spectra were measured on a JEOL-FX60Q Fourier transform NMR spectrometer. Tetramethylsilane was the internal reference. Mass spectra were determined at 70 eV on a Finnigan 4023 GC/MS system. "Flash chromatography" refers to the technique developed by Still.[14] Thin-layer chromatography was performed on precoated (0.2 mm) silica gel 60 F_{254} plastic sheets (E. Merck). These plates were permanently developed by spraying with a solution of 3% aqueous ceric ammonium sulfate in 10% sulfuric acid followed by brief heating. The alkyllithium reagents were standardized by titration against 2,5-dimethoxybenzyl alcohol.[15] Tetrahydrofuran was distilled from sodium/benzophenone and diisopropylamine was distilled over sodium hydride. Lithium diisopropylamide was prepared as described previously.[8] All reactions were performed in oven-dried (130 °C) glassware under prepurified argon.

3-Iodoindole (5). To a magnetically stirred solution of indole (2.00 g, 17.0 mmol) in dry THF (30 mL) under argon at −78 °C was added dropwise via syringe over 3 min *n*-butyllithium (1.6 M in hexane; 11.0 mL, 17.6 mmol). The mixture was warmed to 20 °C and stirred for 1 h. The resulting lithioindole partially precipitated as a white solid in a colorless solution. To a separate three-neck round-bottom flask fitted with an internal thermometer, rubber septum, magnetic stirring bar, and argon inlet adapter were added iodine (4.34 g, 17.9 mmol) and dry THF (60 mL). This solution was cooled to −78 °C and with vigorous stirring the

(12) Parrot, J.; Hervieu, J.; Ursy, Y.; Paty, M. *Bull. Soc. Chim. Fr.* **1964**, *5*, 1063.
(13) (a) Muller, H. Dissertation Organisch-Chemisches Institut der Universität, Heidelberg, Germany, 1963. (b) Bergman, J.; Eklund, N. *Tetrahedron* **1980**, *36*, 1439. (c) Wittig, G. *Pure Appl. Chem.* **1963**, *7*, 173.
(14) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(15) Winkle, M. R.; Lansinger, J. M.; Ronald, R. C. *J. Chem. Soc., Chem. Commun.* **1980**, 88.
(16) Hino, T.; Nakamura, T.; Nakagawa, M. *Chem. Pharm. Bull. Jpn.* **1975**, *23*, 2990.

lithioindole was added dropwise over 10–15 min via a wide-bore transfer needle. This mixture was stirred at −78 °C for 2 h and warmed to 0 °C, and the THF was partially removed in vacuo with minimal heating. Ether (100 mL) and cold deoxygenated water (50 mL) were added and the contents were stirred at 0 °C for 20 min in the dark. The organic phase was separated, dried (Na_2SO_4), and concentrated in vacuo to afford an essentially quantitative yield of light tan crystals: crude mp 53–56 °C dec. This material is extremely unstable and should be used immediately.

1-(Phenylsulfonyl)-3-iodoindole (6). To a solution of indole (6.00 g, 51.2 mmol) in dry THF (75 mL) cooled to −78 °C under argon and mechanically stirred in the upper reaction vessel (Figure 1) was added *n*-butyllithium (1.58 M in hexane; 33.1 mL, 52.2 mmol) via syringe over 5 min. The milky white suspension which resulted was warmed to −10 °C over 1.5 h and then slowly dripped into a −78 °C solution of iodine (13.3 g, 52.2 mmol) in dry THF (75 mL) over 15 min with vigorous magnetic stirring maintained in the lower flask. This solution was warmed to 0 °C over 2 h, treated with a drop of methanol, and cooled to −78 °C over 0.5 h. The resulting solution of 3-iodoindole was then treated at −78 °C over 1–2 min with a solution of lithium diisopropylamide prepared in the upper flask from diisopropylamine (5.29 g, 52.3 mmol) and *n*-butyllithium (1.58 M in hexane; 32.4 mL, 51.2 mmol) in dry THF (20 mL). The light-orange reaction mixture which resulted was stirred at −78 °C for 25 min and then quenched with benzenesulfonyl chloride (9.50 g, 53.8 mmol) neat via syringe over 1 min. After warming to room temperature overnight, the reaction mixture was cooled to 5 °C, poured into 2% aqueous sodium bicarbonate (500 mL), and extracted with ether (3 × 300 mL). The combined extracts were washed with 3% aqueous sodium thiosulfate (1 × 250 mL), H_2O (2 × 200 mL), and brine (2 × 250 mL), dried (Na_2SO_4), and rotary evaporated to afford 20.0 g of light-purple crystals. Chromatography over Florisil (1:1 ether–hexane) gave 17.2 g (88% from indole) of analytically pure **6**, as a colorless solid: mp 125–127 °C; IR ($CHCl_3$) 1580 (m), 1450 (s), 1380 (s), 1270 (s), 1175 (s), 1130 (s), 1020 (s), 925 (s), 680 (m), 585 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 8.10–7.80 (m, 3 H), 7.72 (s, 1 H), 7.55–7.20 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 137.9, 134.3, 133.9, 132.3, 129.6, 129.3, 126.7, 125.6, 123.9, 121.9, 113.3, 67.0; UV (95% EtOH) λ_{max} 217.5 nm, 255, 285 (sh), 293.

Anal. Calcd for $C_{14}H_{10}NO_2SI$: C, 43.88; H, 2.63; N, 3.66; S, 8.37; I, 33.12. Found: C, 43.92; H, 2.65; N, 3.66; S, 8.33; I, 33.05.

A maximum yield of 66% was obtained when **5** was isolated and then treated with (1) LDA/THF and (2) benzenesulfonyl chloride to afford **6**.

1-(Phenylsulfonyl)indole (8). To a solution of indole (22.50 g, 0.1921 mol) in dry THF (150 mL) under argon at −78 °C was added dropwise via syringe over 15 min *n*-butyllithium (1.58 M in hexane; 128 mL, 0.202 mol). The cooling bath was removed and the solution was stirred for 1 h while warming to 0 °C. The resulting indole anion precipitated as a very fine white solid in a cloudy colorless solution. After the suspension was recooled to −78 °C, benzenesulfonyl chloride (37.31 g, 0.2112 mol) was added neat via syringe over 20 min, keeping the internal temperature below −60 °C. The resulting colorless mixture was allowed to warm slowly to room temperature overnight, poured into 2% aqueous sodium bicarbonate (500 mL), and extracted with Et_2O (4 × 200 mL). The combined extracts were washed with 2% aqueous sodium bicarbonate (1 × 150 mL), H_2O (2 × 100 mL), and brine (2 × 250 mL), dried (K_2CO_3), and evaporated in vacuo to give a light amber oil which crystallized when triturated with 2:1 hexane–ether (80 mL). After standing in the cold for several hours, the product was collected by filtration, washed with hexane, and dried at 45 °C (20 torr) to provide 45.1 g (91%) of pure **8** as colorless crystals: mp 76–76.5 °C (lit.[1] mp 77.5–79 °C); ^{13}C NMR ($CDCl_3$) δ 138.1, 134.7, 133.6, 130.6, 129.1, 126.5, 126.1, 124.5, 123.2, 121.3, 113.3, 109.1.

1-(Trimethylacetyl)indole (9). To a magnetically stirred solution of indole (11.25 g, 0.0960 mol) in dry THF (80 mL) under argon at −78 °C was added via syringe *n*-butyllithium (1.58 M in hexane; 64 mL, 0.10 mol). The cooling bath was removed and the solution was stirred for 1 h while warming to 0 °C. The resulting milky white suspension was then cooled to −75 °C and pivaloyl chloride (12.74 g, 0.1056 mol) was added neat via syringe, keeping the internal temperature below −50 °C. The resulting light-yellow reaction mixture was allowed to warm slowly to room temperature overnight, poured into H_2O (250 mL), and extracted with CH_2Cl_2 (4 × 150 mL). The combined extracts were washed with H_2O (2 × 350 mL) and brine (2 × 350 mL), dried (Na_2SO_4), and concentrated in vacuo to give a light-amber oil which crystallized when triturated with hexane (60 mL) and cooled in a dry ice/acetone bath. The product was collected by filtration, washed with hexane, and dried to give 17.72 g (92%) of pure **9** as colorless needles in two crops, mp 62–63.5 °C. Crystallization from hexane gave the analytical sample: mp 65–66 °C (lit.[9d] mp 63–64 °C); IR (KBr) 1686 (s), 1585 (s), 1535 (s), 1450 (m), 1402 (s), 1310 (s), 1185 (s), 1155 (s), 1070 (s), 1015 (s), 904 (s), 760 (m), 588 (s), 525 (s), 425 cm^{-1} (s); ^1H NMR ($CDCl_3$) δ 8.67–8.45 (m, 1 H), 7.78–7.12 (m, 4 H), 6.58 (d, 1 H, J = 4 Hz), 1.50 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 176.9, 136.7, 129.3, 125.5, 124.9, 123.4, 120.3, 117.2, 108.1, 41.1, 28.6; UV (95% EtOH) λ_{max} 206 nm, 239, 290, 298.

Anal. Calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.60; H, 7.56; N, 6.92.

1-(Phenylsulfonyl)-3-lithioindole (1). A magnetically stirred solution of **6** in dry THF under argon was cooled to −100 °C. This solution was treated rapidly via syringe with 2 equiv of *tert*-butyllithium (2.1 M in pentane) and stirred at −100 °C for 5 min. The resulting light-yellow solution was immediately quenched in situ with the electrophiles listed in Table I and as described in the representative procedure below.

[1-(Phenylsulfonyl)indol-3-yl]phenylmethanol (10c). A magnetically stirred solution of **1** (0.622 mmol) in dry THF (20 mL) at −100 °C under argon was treated rapidly via syringe with freshly distilled benzaldehyde (0.11 g, 1.04 mmol). The mixture was warmed slowly to room temperature over 6 h. The resulting pale-yellow solution was treated with H_2O (150 mL) and CH_2Cl_2 (100 mL). The aqueous phase was acidified with dilute HCl, saturated with sodium chloride, and extracted with additional CH_2Cl_2 (3 × 50 mL). The combined extracts were washed with H_2O (1 × 75 mL) and brine (2 × 75 mL), dried (K_2CO_3), and concentrated in vacuo to afford a colorless oil. Flash chromatography over silica gel (230–400 mesh) with 5% ethyl acetate in methylene chloride gave a viscous oil which was further dried at 0.3 torr to provide 0.200 g (89%) of analytically pure **10c** as a colorless solid: mp 45.5–47.5 °C; IR ($CHCl_3$) 3595 (s), 1600 (s), 1448 (s), 1370 (s), 1270 (s), 1173 (s), 1115 (m), 1000 (s), 968 (s), 905 (s), 580 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 8.14–7.75 (m, 3 H), 7.58–7.00 (m, 12 H), 5.99 (s, 1 H), 2.53 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 141.8, 138.0, 135.6, 133.6, 129.1, 128.8, 128.5, 128.0, 126.6, 126.5, 125.7, 124.7, 123.7, 123.2, 120.5, 113.6, 70.2; UV (95% EtOH) λ_{max} 218 nm, 248, 284 (sh) nm.

Anal. Calcd for $C_{21}H_{17}NO_3S$: C, 69.40; H, 4.72; N, 3.85; S, 8.82. Found: C, 69.48; H, 4.75; N, 3.83; S, 8.77.

1-(Phenylsulfonyl)-2-lithioindole (2). To a solution of lithium diisopropylamide (8.40 mmol) prepared from diisopropylamine (9.00 mmol) and *n*-butyllithium (1.58 M in hexane; 8.40 mmol) in dry THF (20 mL) under argon at −75 °C was added dropwise via syringe over 5 min a solution of **8** (8.01 mmol) in dry THF (22 mL), keeping the internal temperature below −60 °C. The mixture was stirred for 1.5 h below −70 °C and then allowed to warm slowly to 5 °C over 1 h. The resulting bright-red solution was cooled to −78 °C and then treated with the electrophiles listed in Table I and as described in the representative procedure below.

1-[1-(Phenylsulfonyl)indol-2-yl]ethanol (11e). A magnetically stirred solution of **2** (11.66 mmol) in dry THF (40 mL) at −65 °C under argon was treated rapidly via syringe with a solution of freshly distilled acetaldehyde (1.00 g, 22.7 mmol) in dry THF (5 mL). The mixture was allowed to warm slowly to room temperature overnight, poured into 1% aqueous hydrochloric acid (350 mL), and extracted with CH_2Cl_2 (3 × 250 mL). The combined extracts were washed with H_2O (1 × 400 mL) and brine (2 × 400 mL), dried (K_2CO_3), and rotary evaporated to afford a light orange oil. Flash chromatography over silica gel with methylene chloride elution gave a light-amber viscous oil which was further dried at 0.5 torr (60 °C) for 6 h to provide 3.28 g (93%) of analytically pure **11e** as colorless crystals: mp 101–102 °C; IR (KBr) 3295 (broad s), 1585 (s), 1563 (s), 1448 (s), 1370 (s), 1300 (s), 1173 (s), 1148 (s), 1072 (m), 1005 (m), 915 (s), 822 (s), 740 (m), 680 (s), 652 (s), 620 (s), 595 (s), 570 (s), 560 (s), 517 cm^{-1} (s); ^1H NMR ($CDCl_3$) δ 8.22–7.04 (m, 9 H), 6.64 (s, 1 H), 5.36 (m, 1 H),

3.54 (d, 1 H, J = 5 Hz), 1.64 (d, 3 H, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 144.8, 138.2, 137.0, 133.6, 129.0, 125.9, 124.7, 123.7, 120.9, 114.5, 108.7, 62.5, 21.7; UV (95% EtOH) λ_{max} 222 nm, 251.

Anal. Calcd for $C_{16}H_{15}NO_3S$: C, 63.77; H, 5.02; N, 4.64; S, 10.64. Found: C, 63.69; H, 5.06; N, 4.59; S, 10.61.

1-(Phenylsulfonyl)-2,3-diiodoindole (13). To a solution of lithium diisopropylamide prepared from diisopropylamine (0.68 g, 6.69 mmol) and *n*-butyllithium (1.58 M in hexane; 3.83 mL, 6.05 mmol) in dry THF (30 mL) under argon at −78 °C was added via syringe over 3 min a solution of **6** (2.25 g, 5.87 mmol) in dry THF (25 mL). After being stirred for 1.5 h at −78 °C, the golden yellow solution was treated dropwise over 4 min with a solution of iodine (1.91 g, 7.53 mmol) in dry THF (20 mL) and the mixture was allowed to warm slowly to room temperature overnight. The reaction mixture was cooled to 0–5 °C and treated with 5% aqueous sodium thiosulfate (200 mL) and CH_2Cl_2 (200 mL). The layers were separated, and the organic phase was washed again with sodium thiosulfate (150 mL). The combined aqueous portions were extracted with CH_2Cl_2 (2 × 100 mL) and the combined organic extracts were washed with water (2 × 150 mL) and brine (2 × 150 mL), dried (Na_2SO_4), and evaporated in vacuo to give 3.35 g of crude **13** as a light-tan crystalline solid. Column chromatography over Florisil with 1:1 ether–hexane afforded 2.93 g (98%) of analytically pure **13** as a colorless crystalline solid: mp 166–167 °C; IR ($CHCl_3$) 1585 (m), 1450 (s), 1435 (s), 1380 (s), 1265 (s), 1180 (m), 1140 (s), 1085 (s), 1020 (s), 935 (m), 675 (m), 585 cm^{-1} (m); ^{1}H NMR ($CDCl_3$) δ 8.28–7.73 (m, 3 H), 7.58–7.05 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 138.0, 137.8, 134.1, 133.4, 129.1, 127.1, 125.8, 124.6, 122.5, 115.5, 90.4, 88.5; UV (95% EtOH) λ_{max} 210 nm, 266.

Anal. Calcd for $C_{14}H_9NO_2SI_2$: C, 33.03; H, 1.78; N, 2.75; S, 6.30; I, 49.85. Found: C, 33.04; H, 1.81; N, 2.73; S, 6.25; I, 49.85.

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Supplementary Material Available: Detailed experimental procedures for the compounds listed in Table I (12 pages). Ordering information is given on any current masthead page.

Pyrido[2,3-*d*]pyrimidines. Synthesis of the 5-Deaza Analogues of Aminopterin, Methotrexate, Folic Acid, and N^{10}-Methylfolic Acid

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Reaction of bromoacetic acid with *N,N*-dimethylformamide and phosphorus oxychloride gave a triformylmethane derivative, which was condensed with 2,4-diaminopyrimidin-6(1*H*)-one (**2**) in water at reflux to give 2-amino-4(3*H*)-oxopyrido[2,3-*d*]pyrimidine-6-carboxaldehyde (**4**). The structure of **4** was confirmed by conversion to the 2,4-dinitrophenylhydrazone and oxidation to the known 6-carboxylic acid (**6**). Similarly, condensation of **1** with 2,4,6-triaminopyrimidine gave 2,4-diaminopyrido[2,3-*d*]pyrimidine-6-carboxaldehyde (**5**). Reductive alkylation of diethyl (*p*-aminobenzoyl)-L-glutamate (**9**) with **5** in 70% acetic acid over Raney nickel gave diethyl *N*-[4-[[(2,4-diaminopyrido[2,3-*d*]pyrimidin-6-yl)methyl]amino]benzoyl]-L-glutamate (**10**), which was saponified with base to give the corresponding glutamic acid **11** (5-deazaaminopterin). The latter was methylated with formaldehyde and sodium cyanoborohydride to give 5-deazamethotrexate (**12**). Reductive alkylation of **9** with **4** gave diethyl *N*-[4-[[(2-amino-4(3*H*)-oxopyrido[2,3-*d*]pyrimidin-6-yl)methyl]amino]benzoyl]-L-glutamate (**13**), which was converted to the corresponding glutamic acid **14** (5-deazafolic acid). The preferred route for the preparation of **14** involved the hydrolysis of **10** with base at reflux, which resulted in replacement of the 4-amino group and saponification of the ester groups. Methylation of **14** with formaldehyde and sodium cyanoborohydride gave 5-deaza-10-methylfolic acid (**15**), which was also prepared by alkaline hydrolysis of the 4-amino group of **12**.

Aminopterin and methotrexate are folic acid antagonists that inhibit the enzyme dihydrofolate reductase.[1] In addition, quinazoline (5,8-dideazapteridine) analogues of folic acid, aminopterin, and methotrexate have been identified as potent inhibitors of both dihydrofolate reductase and thymidylate synthetase.[2] In another series, 2,4-diaminopyrido[2,3-*d*]pyrimidines (5-deazapteridines) are known to be dihydrofolate reductase inhibitors.[3] The synthesis of 5-deazafolic acid via a condensation reaction involving triformylmethane has been reported,[4] and the preparation of 5-deazaaminopterin via a long sequence of reactions involving the elaboration of either a pyridine[5]

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