

Reaction of 1-Protected-indoles with Pyridine Substrates

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The products resulting from the reactions of 1-benzenesulfonyl-2-lithioindole and 2-lithio-1-methylindole with different pyridine substrates (pyridine, 1-methoxy-pyridinium salt and 2-bromopyridine) have been studied. The use of lithiocyclohexylisopropylamide as a lithiating agent of indoles has been investigated. The preparation of four of the possible benzenesulfonyl derivatives of 2-(2'-pyridyl)indole is described.

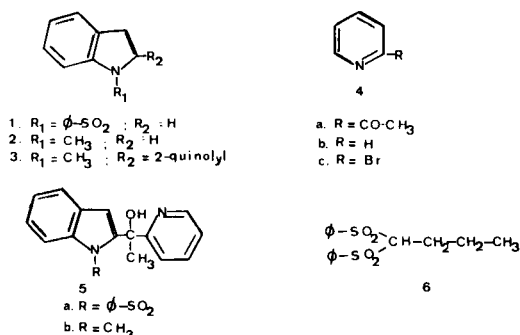
J. Heterocyclic Chem., **16**, 1631 (1979).

Due to an interest in the preparation of 1-benzenesulfonyl-2-(2'-pyridyl)indoles, and since 2-lithioindoles could provide a synthetic route to 2-substituted indoles, we now report the results obtained in the reactions of the lithiated derivative of 1-benzenesulfonylindole **1** with different pyridine substrates. In certain cases we found it convenient to effect this type of reaction with 1-methylindole **2**, since it was demonstrated that 2-lithio-1-methylindole could be efficiently converted into 1-methyl-2-(2'-quinoly)indole **3** by reaction with quinoline (1). Likewise, Hamanaec and Kumadaki (2) have obtained compound **3** by condensation of the same lithio derivative with 2-chloroquinoline.

On the other hand, almost as soon as organolithium compounds became available it was discovered that they react with pyridine to give 2-substituted derivatives. Thus, Gilman and Edward (3) have described the preparation of several 2-arylpiperidines in satisfactory yields by adding aryllithium compounds to pyridine. More recently (4) it has been demonstrated that 1-benzenesulfonylindole **1** can be lithiated in the 2-position.

In the preparation of lithiated derivatives, the lithiating agents of more frequent use are *n*-butyllithium or *t*-butyllithium (4,5). In our work, instead of *t*-butyllithium, we tested the use of lithiocyclohexylisopropylamide as a lithiating agent. This reagent was used to obtain the ester enolates and it appears to be an appropriate reagent for the lithiation of **1**.

Scheme 1



The lithiation of compound **1** with *n*-butyllithium and with lithiocyclohexylisopropylamide was achieved by controlling the quantity of the compound lithiated through the percentage of product obtained in the reaction with the pyridine compound **4a**. Generally, the reaction of 2-lithioindoles with any pyridine substrate takes place by adding the latter compounds to a reaction mixture of the lithiating reagent and the indole derivative. The results obtained from using both lithiating agents are shown in Table I.

The addition of **4a** at room temperature with stirring and under a nitrogen atmosphere to the reaction mixture of compound **1** and *n*-butyllithium enabled us to isolate carbinol **5a** (9%). The major product (56%) formed in this reaction proved to be compound **6**, based on spectroscopic data and combustion analysis. The formation of 1,1'-dibenzenesulfonylbutane **6** could be explained by the reaction of *n*-butyllithium with the benzenesulfonyl group formed by cleavage of the nitrogen-sulfur bond (6). It is known that the benzenesulfonyl group can be removed under alkaline conditions.

Since these results indicated that the lithiated compound had been formed in small quantity, we changed the preparative conditions and reacted the substrates (compound **1** and *n*-butyllithium) overnight in ether under reflux. The addition of **4a** led to the same results. With the use of lithiocyclohexylisopropylamide as a lithiating agent for **1** and the subsequent addition of **4a**, compound **5a** was obtained in 71% yield without the isolation of **6**.

By contrast, 1-methylindole **2** could not be lithiated with lithiocyclohexylisopropylamide; it was, however, efficiently lithiated with *n*-butyllithium (1). Thus, the carbinol **5b** was obtained in 40% yield by addition of compound **4a**. The non-metallation of **2** with lithiocyclohexylisopropylamide could be due to the differing acidities of the C₂ indole hydrogen atom in compounds **1** and **2**.

Later, we tested the reactivity of the lithio derivative of **1** with pyridine **4b**. In all the experiments (7a-e), the addition of pyridine took place at low temperature with stirring under a nitrogen atmosphere. No 1-benzenesulfonyl-2-

Table I

Indolic Compound	Lithiating Agent	Product Control Lithiation	By-Product
1	<i>n</i> -Butyllithium	Compound 5a (90%)	Compound 6 (56%)
2	<i>n</i> -Butyllithium (a)	Compound 5b (40%)	_____
1	Lithiocyclohexylisopropylamide	Compound 5a (71%)	_____
2	Lithiocyclohexylisopropylamide (b)(c)	_____	_____

(a) Solvent: ether, 8 hours at reflux. (b) Solvent: ether-tetrahydrofuran, overnight at room temperature. (c) Solvent: ether-tetrahydrofuran, 8 hours at reflux.

(2'-pyridyl)indole **7a** could thus be isolated. The reaction of 2-lithio-1-methylindole with pyridine gave the same result (cf. Schemes 2 and 3).

Since nucleophilic substitution reactions on an unactivated pyridine ring are facilitated by quaternization, we tested the condensation with 1-methoxypyridinium methylsulphate **8**, which is very reactive toward the usual nucleophilic reagents. As can be seen in Table II, compound **7a** was not isolated. The formation of carbinol **9** in variable yield could be explained by the reaction of the lithio derivative of **1** with the formaldehyde obtained from the decomposition of the 1-methoxypyridinium salt **8** (8,9) (cf. Scheme 2).

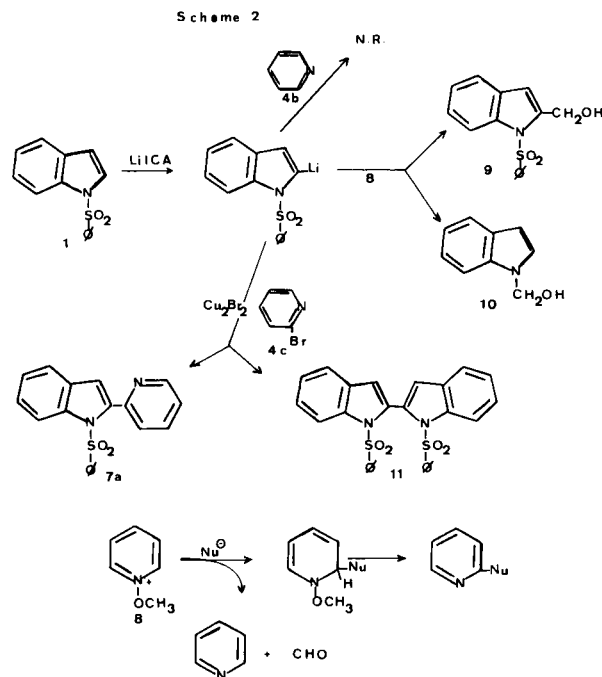
Under more drastic conditions (assay 4, Table II) two new products were observed, besides **9**: the indole and the carbinol **10**. The indole was probably formed by cleavage of the nitrogen-sulfur bond of compound **1**. The reaction of indole with formaldehyde (proceeding from the 1-methoxypyridinium salt) gave compound **10**. Compounds **9** and **10** were obtained in the ratio 10:1 (by glc). Their separation could not be completely achieved either by column chromatography or by fractional crystallization.

The structure of **10** was determined by nmr spectral data. Thus, compound **9** (major component, lowest glc retention time) showed a signal at δ 4.8 due to the C₂-CH₂-OH group and one singlet at δ 6.6 due to the C₃-H, whereas compound **10** (minor component, longest glc retention time) showed a signal at δ 5.5 due to the N-CH₂-OH group and one doublet at δ 6.5 ($J = 0.5$) due to the C₃-H.

Table II

Assay (a)	Molar Ratio (b)	Temperature of Addition	Product (%)
1	1:1	18°	9 (21%)
2	1:3	-10°	9 (15%)
3	1:1	-10° (c)	9 (18%)
4	2:1	65°	9 (18%), 10 (2%)

(a) Tetrahydrofuran was used in all cases. (b) Lithiated derivative of **1**: compound **8**. (c) Subsequent reflux in tetrahydrofuran.



In a further attempt to achieve our objective, we proceeded to use a different pyridine substrate, namely, 2-brominepyridine **4c**. In the reaction of **4c** with the organocuprous lithium compound (**10**), which originated from the reaction of the lithio derivative of **1** at -70° with cuprous bromide, a white solid was isolated in 15% yield. Its spectra is in good agreement with the structure of compound **7a**. Among the by-products, 1,1-dibenzensulfonyl-2,2'-bisindole **11** (3%) was identified from the available data. The formation of this compound is to be expected in this type of reaction (11).

The same reaction using 1-methylindole **2**, instead of **1** gives two products of high molecular weight, whose structures have not yet been established. The product of condensation, **7b**, was not formed (cf. Scheme 3).

Simultaneously, we tested the preparation of compound **7a** by the reaction of 2-(2'-pyridyl)indole **7c** (12a,12b) with benzenesulfonyl chloride by Heaney's method (13). In our hands, this method gave excellent yields (80-95%) of various 1-protected indoles (cf. Scheme 4). In this reaction, a white solid, compound **12**, was isolated in 14% yield.

The structure of this compound was determined by spectral data.

The availability of the nmr spectra of 1-benzenesulfonyl-6-nitroindole **13a** and 6-nitroindole **13b** (compounds obtained for other purposes), the position of the C₅H and C₇H proton signals of the indole compound are shown in Table III, and the measurement of the relative intensities of the absorptions for each sample enabled us to identify compound **12** as 6-benzenesulfonyl-2-(2'-pyridyl)indole (Scheme 4). In Table III, the chemical shift for the C₃-H proton is also shown.

The chemical shifts produced by the benzenesulfonyl group over the aromatic protons has been estimated from the spectrum of the benzenesulfonylchloride: 0.73 ppm at low-field for the *ortho* protons and 0.43 for the *para* protons. The chemical shift value of the C₇-H proton has been estimated from the spectra as 0.45-0.55 ppm at low-field (with respect to indole), when the 1-position is substituted by the benzenesulfonyl group. When the 2-pyridyl position is substituted, the chemical shift value of the C₇-H proton produced a low-field shift of about 0.33 ppm.

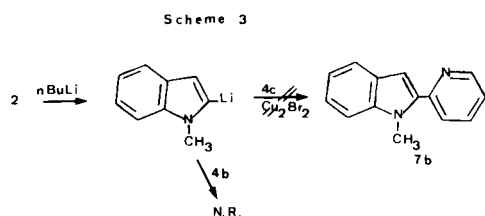


Table III

Chemical Shift in Deuteriochloroform (Values) (a)

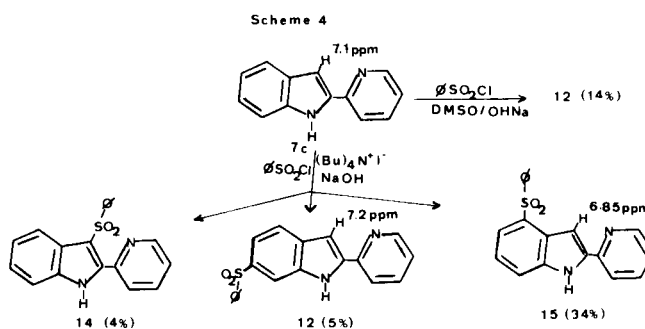
Indole Compound	Chemical Shift (ppm)			Coupling Constants J in Hz
	C ₃ -H	C ₅ -H	C ₇ -H	
1	6.51 dd	(7.38) m (b)	7.85 m	J ₃₋₂ = 3.3, J ₃₋₇ = 0.7
7a	7.15 d (c)	(7.62) m	8.33 m	J ₃₋₇ = 0.7
7c	7.1 d (c)	7.20 m	7.7 m	J ₃₋₇ = 0.7
13a	6.75 dd	8.1 dd	8.85 m	J ₃₋₂ = 3.2, J ₃₋₇ = 0.7 J ₅₋₄ = 3.1, J ₅₋₇ = 1.1
13b	6.71 dd	8.05 dd	8.4 m	J ₃₋₂ = 3.1, J ₃₋₇ = 0.7 J ₅₋₄ = 3.2, J ₅₋₇ = 1.1

(a) Abbreviations: dd = double doublet, m = multiplet, d = doublet.

(b) Figures in parentheses are tentative assignments. (c) Due to the small value of J₃₋₇, this signal is described as a singlet.

In view of these results, we finally tested the benzenesulfonation of **7c** in the presence of sodium hydroxide and a catalytic amount of *N*-tetrabutylammonium iodide. This method, which has been slightly modified by us, has been used by Survorov, *et al.*, (14), for the preparation of *N*-alkylindoles.

The addition, at room temperature, of benzenesulfonyl chloride in benzene to a mixture of **7c** in benzene, ammonium salt and 50% sodium hydroxide, gave a mixture



of several products. Separation of this crude mixture was achieved by chromatography on a silica gel column giving three isomeric products: 6-benzenesulfonyl-2-(2'-pyridyl)indole **12**, 3-benzenesulfonyl-2-(2'-pyridyl)indole **14**, and 4-benzenesulfonyl-2-(2'-pyridyl)indole **15**. Spectral data and analyses were consistent with the suggested structures. The ir spectra showed the absorption of the NH group. The nmr spectrum of compound **14** indicated: (i) a multiplet at 8.75 ppm (1H) due to the C₆-H pyridine proton and (ii) two multiplets at 7.7 ppm (6H) and 7.35 ppm (7H), thus confirming the suggested structure. The downfield shift of the benzenoid signals is due to the deshielding effect of the benzenesulfonyl group attached to the 3-position.

On the other hand, the abnormal absorption position for the C₃-H proton in the nmr spectrum of compound **15** enabled us to identify it as the 4-isomer. The deshielding effect of the benzenesulfonyl group on the benzenoid ring not only affects the neighboring protons in the carbocyclic ring, but also shifts the signals of the heterocyclic ring downfield. By contrast, the absorption position for the C₃-H proton shows a shielding effect (6.85 ppm instead of 7.1-7.3 ppm). It seems reasonable to assume that the difference observed is probably due to the diamagnetic anisotropy of the substituent in the 4-position. An examination of molecular models reveals that this proton is sterically held below the plane of the aromatic nucleus of the benzenesulfonyl group.

Furthermore, the spectrum of compound **15** showed: (i) a multiplet at 8.65 ppm (1H) due to the C₆-H pyridine proton (ii) a multiplet at 8.24 ppm (1H) due to the C₇-H indole proton, and (iii) a multiplet at 8.15 ppm (1H) expected for the C₅-H indole proton.

After theoretical considerations of the nmr spectra of the 5- and 7-isomers, it was possible to discard them. Considerations concerning the differentiation between attack at the 3-, 4-, or 6-position on compound **7c**, and theoretical work aimed at studying the ability of nucleophiles to initiate ring attack on pyridine and its derivatives have been realized.

EXPERIMENTAL

Melting points were determined on a Büchi apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded on a Perkin-Elmer R-12B spectrometer and deuteriochloroform as solvent unless otherwise indicated. Chemical shifts are reported as δ values in parts per million (ppm). Elemental analyses were performed by Instituto de Química Organica, Barcelona.

Preparation of 1.

1-Benzenesulfonylindole (**1**) was obtained by Heaney's method (13).

Lithiation of **1**. Reaction of the Lithiated Derivative of **1** with **4a**.

A. With *n*-Butyllithium.

A solution of 1-benzenesulfonylindole (**1**) (10 mmoles) in ether was cooled to -12° . *n*-Butyllithium (17 ml. of a 0.75M solution) was added under an atmosphere of dry nitrogen and the reaction mixture was allowed to warm to room temperature with stirring for 30 minutes. A solution of 11 mmoles of 2-acetylpyridine (**4a**) in ether was added dropwise. The reaction mixture was stirred overnight at room temperature, after which time the solution was diluted. The ether extract was dried and evaporated. Chromatography of the product on a silica gel column eluted with benzene-chloroform gave 0.35 g. (9%) of compound **5a**, 1-benzenesulfonyl-2-[α -hydroxy- α -(2'-pyridyl)ethyl]indole, m.p. 138-140°, recrystallized from benzene; nmr: 8.4 (m, 1, C₆-H pyridine), 8 (m, 1, C₇-H indole), 7.35 (m, 11, C-H aromatic and pyridine), 7 (s, 1, C₃-H indole), 5.7 (broad signal, 1, -OH), 1.95 (s, 3, C-CH₃).

Anal. Calcd. for C₂₁H₁₈N₂O₂S: C, 66.66; H, 4.80; N, 7.40; S, 8.45. Found: C, 66.87; H, 4.88; N, 7.45; S, 8.20.

On elution with benzene-chloroform (5:5), 0.94 g. (56%) of compound **6**, 1,1-dibenzenesulfonylbutane was obtained, m.p. 134-135°, recrystallized from benzene; nmr 7.6 (m, 10, C-H aromatic ring), 4.4 (t, 1, C₁-H), 2.1 (c, 2, C₁-CH₂), 1.55 (m, 2, C₂-CH₂), 0.8 (t, 3, C₃-CH₃).

Anal. Calcd. for C₁₆H₁₆O₂S₂: C, 56.80; H, 5.36; S, 18.92. Found: C, 56.76; H, 5.35; S, 18.79.

B. With Lithiocyclohexylisopropylamide.

A solution of cyclohexylisopropylamide (2.2 ml., 13 mmoles) in tetrahydrofuran was cooled in an ice-bath and 10 ml. of 0.6 M *n*-butyllithium was added dropwise for 10 minutes. The reaction mixture was stirred at 0° for 30 minutes, after which time a solution of 10 mmoles of **1** in tetrahydrofuran was added. The temperature of addition was -20° . The reaction mixture was then allowed to warm to room temperature. To this solution was added 10 mmoles of a solution of **4a** in tetrahydrofuran. The solution was stirred for 12 hours and then poured into water. After isolation by extraction with ether, 2.68 g. (71%) of compound **5a** was obtained.

1-Methyl-2-[α -hydroxy- α -(2'-pyridyl)ethyl]indole (**5b**).

To a solution of 2-lithio-1-methylindole (**1**) at 0° and under an atmosphere of nitrogen, 10 mmoles of a solution of **4a** in tetrahydrofuran was added. The reaction mixture was allowed to stir at room temperature for 45 minutes and then poured into excess water and extracted thoroughly with ether. The combined ether extracts were washed with dilute hydrochloric acid, dried and evaporated to give the crude product. The compound **5b** (414 mg., 40%) was obtained from hexane as a yellow solid, m.p. 117-118°; nmr: 8.4 (m, 1, C₆-H pyridine), 7.4 (m, 7, C-H aromatic and pyridine), 6.7 (s, 1, C₃-H), 5.2 (broad signal, 1, -OH), 3.35 (s, 3, N-CH₃), 1.95 (s, 3, C-CH₃).

Anal. Calcd. for C₁₆H₁₆N₂O: C, 76.16; H, 6.39; N, 11.10. Found: C, 76.08; H, 6.42; N, 10.95.

1-Benzenesulfonyl-2-hydroxymethylindole (**9**).

A solution of 1-benzenesulfonyl-2-lithioindole was added dropwise to a solution of 1-methoxypyridinium methylsulphate (**8**) in tetrahydrofuran under an atmosphere of nitrogen and the reaction mixture was allowed to stir for 24 hours. The resulting solution was hydrolyzed and extracted with methylene chloride. The organic layer was dried and the solvent removed giving a residue, which was purified by chromatography on a

silica gel column. On elution with benzene-chloroform, 587 mg. (21%) of compound **9**, m.p. 74°, was obtained; nmr: 7.9 (m, 3, C-H aromatic), 7.3 (m, 6, C-H aromatic), 6.61 (s, 1, C₃-H), 4.86 (s, 2, C₂-CH₂) 3 (s, 1, -OH).

Anal. Calcd. for C₁₅H₁₃NO₂S: C, 62.71; H, 4.56; N, 4.88; S, 11.12. Found: C, 62.54; H, 4.44; N, 4.73; S, 11.11.

1-Benzenesulfonyl-2-(2'-pyridyl)indole (**7a**).

To a solution of 25 mmoles of 1-benzenesulfonyl-2-lithioindole in ether, was added (keeping the temperature at -70°) 1.79 g. (12.5 mmoles) of cuprous bromide previously dried at 100° for 24 hours. This solution was then allowed to stir for 30 minutes. Then, 10 mmoles of 2-bromopyridine **4c** in tetrahydrofuran was added at -40° . When the addition was completed, the mixture was maintained at 0° for 3 hours; the solvent was then distilled and toluene was added. This new solution was refluxed for 2 hours. After cooling, 100 ml. of nitrobenzene was added. The resulting solution was stirred for 30 minutes at room temperature and then was poured into aqueous ammonium chloride and extracted with benzene. The organic layer was extracted with 10% hydrochloric acid solution, the nitrobenzene distilled and the residue purified by chromatography on a silica gel column. On elution with benzene, 350 mg. (3%) of a substance was obtained which was identified as 1,1'-bis(benzenesulfonyl)-2,2'-biindole **11**, m.p. 277-278°; nmr: 8.2 (m, 6, C-H aromatic), 7.4 (m, 12, C-H aromatic), 6.7 (s, 2, C₃-H).

Anal. Calcd. for C₂₈H₂₀N₂O₄S₂: C, 65.62; H, 3.93; N, 5.47; S, 12.49. Found: C, 65.43; H, 4.01; N, 5.37; S, 12.41.

The aqueous layer was basified with 10% potassium hydroxide solution and extracted with ether. One solid (400 mg., m.p. 117-119°) separated from the organic layer and was identified as compound **7a**; nmr: 8.45 (m, 1, C₆-H pyridine) 8.33 (m, 1, C₇-H indole), 7.55 (m, 4, C-H aromatic and pyridine), 7.25 (m, 7, C-H aromatic and pyridine), 7.15 (s, 1, C₃-H indole).

Anal. Calcd. for C₁₉H₁₄N₂O₂S: C, 68.25; H, 4.22; N, 8.38; S, 9.57. Found: C, 68.33; H, 4.30; N, 8.35; S, 9.52.

2-(2'-Pyridyl)indole (**7c**).

By adding 2-acetylpyridine (**4a**) to a solution of phenylhydrazine in ethanol, the phenylhydrazone of **4a** was obtained. The phenylhydrazone (471 mmoles) was heated with 34.5 g. of polyphosphoric acid in an oil-bath at 160° for 15 minutes. The reaction mixture was hydrolyzed and basified with sodium hydroxide. A precipitate was formed which was purified by sublimation. A yellow solid, **7c**, m.p. 152° (35%) was obtained; nmr: 8.5 (m, 1, C₆-H pyridine) 7.7 (m, 2, C₇-H indole, C₄-H pyridine), 7.20 (m, 5, C-H aromatic and pyridine), 7.1 (s, 1, C₃-H indole).

Anal. Calcd. for C₁₃H₁₀N₂: C, 80.38; H, 5.19; N, 14.42. Found: C, 80.15; H, 5.03; N, 14.40.

6-Benzenesulfonyl-2-(2'-pyridyl)indole (**12**).

To a solution of 5.60 g. of potassium hydroxide in 10 ml. of dimethylsulphoxide, 25 mmoles of **7c** in 100 ml. of dry ether was added. The resulting mixture was stirred at room temperature for 1 hour and then poured into excess water and extracted with ether. The ether extracts were washed, dried and evaporated to give the crude product. Chromatography of the crude product on a silica gel column, on elution benzene, gave 115 mg. (14%) of compound **12**, m.p. 111-112°; nmr: 8.7 (m, 1, C₆-H pyridine), 8.5 (m, 2, C₇-H and C₃-H indole), 7.7 (m, 4, C-H aromatic and pyridine), 7.35 (m, 6, C-H aromatic and -NH indole), 7.2 (s, 1, C₃-H).

Anal. Calcd. for C₁₉H₁₄N₂O₂S: C, 68.25; H, 4.22; N, 8.38; S, 9.57. Found: C, 68.20; H, 4.22; N, 8.18; S, 9.50

3-Benzenesulfonyl-2-(2'-pyridyl)indole (**14**) and 4-Benzenesulfonyl-2-(2'-pyridyl)indole (**15**).

A solution of 4.50 g. (26 mmoles) of benzenesulfonyl chloride in 25 ml. of benzene was added dropwise to a vigorously stirred mixture of 3.30 g. (17 mmoles) of **7c**, 0.31 g. (8.4 mmoles) of tetrabutylammonium iodide, 100 ml. of benzene and 15 ml. of 50% sodium hydroxide solution. The mixture was stirred at room temperature for 8 hours and then it was diluted with 25 ml. of water. The organic layer was separated, washed

with water, dried over anhydrous magnesium sulphate and the benzene was removed by distillation. The remaining residue was chromatographed on a silica gel column. On elution with benzene-chloroform, the following products were obtained: 0.310 g. (5%) of compound **12**, 0.230 g. (4%) of compound **14**, m.p. 136°, and 1.911 g. (34%) of compound **15**, m.p. 125°.

Compound **14** had nmr as follows: 8.75 (m, 1, C₆-H pyridine), 7.7 (m, 6, C-H aromatic and NH indole, C-H pyridine), 7.35 (m, 7, C-H aromatic).

Anal. Calcd. for C₁₅H₁₄N₂O₂S: C, 68.25; H, 4.22; N, 8.38; S, 9.57. Found: C, 68.15; H, 4.22; N, 8.20; S, 9.50.

Compound **15** had nmr as follows: 8.65 (m, 1, C₆-H pyridine), 8.25 (m, 1, C₇-H indole), 8.15 (m, 1, C₅-H indole), 7.7 (m, 4, C-H aromatic and pyridine), 7.35 (m, 6, C-H aromatic, NH indole and C-H pyridine), 6.85 (s, 1, C₃H indole).

Anal. Calcd. for C₁₅H₁₄N₂O₂S: C, 68.25; H, 4.22; N, 8.38; S, 9.57. Found: C, 68.20; H, 4.22; N, 8.35; S, 9.55.

1-Benzenesulfonyl-6-nitroindole (**13a**) and 6-nitroindole (**13b**).

The nitration of compound **1** with 25 ml. of nitric acid at 30° for 1 hour gave 30% of compound **13a**, m.p. 197°; nmr: 8.85 (m, 1, C₇-H indole), 8.1 (C₅-H indole), 7.8 (m, 4, C-H benzenoid), 7.5 (m, 3, C₂-H indole and C-H benzenoid), 6.75 (C₃-H).

Anal. Calcd. for C₁₄H₁₀N₂O₄S: C, 55.63; H, 3.34; N, 9.27; S, 10.58. Found: C, 55.60; H, 3.33; N, 9.15; S, 10.55.

When a solution of **13a** in methanolic sodium hydroxide was heated at reflux for 8 hours, cooled and concentrated, a solid was obtained which was purified on an alumina column. A substance, **13b**, m.p. 141° was isolated (15); nmr: 8.4 (m, 1, C₇-H), 8.05 (dd, C₅-H), 7.95 (dd, C₄-H), 7.8 (NH), 7.67 (C₂-H), 6.71 (C₃-H).

Anal. Calcd. for C₈H₆N₂O₂: C, 59.26; H, 3.73; N, 17.28. Found: C, 59.15; H, 3.77; N, 17.30.

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