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A New Indole Synthesis *via* Rearrangements of N-Propargylaniline N-Oxides. A One-pot Synthesis of Indole-3-acetonitriles

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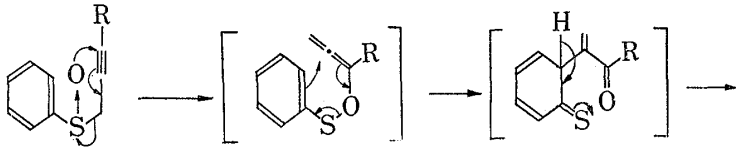
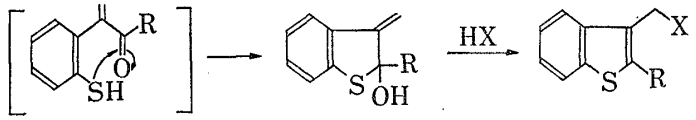
A new, general method was developed for the synthesis of 3-(substituted-methyl)-indoles from N-propargylanilines. The method involves oxidation of the aniline with *m*-chloroperbenzoic acid and subsequent treatment with a suitable nucleophilic reagent under mild conditions in a single flask. The possible pathway was indicated to be (a) formation of an N-oxide, (b) [2,3] and [3,3] sigmatropic rearrangements of a propargyl group, (c) formation of a 3-methylideneindolenine intermediate, and (d) an attack of a nucleophilic reagent on the methylidene function.

The process was quite general and provided a new route for synthesizing 3-(substituted-methyl)indoles—for example, indole-3-acetonitriles, 3-phenylthiomethylindoles, 3-azidomethylindoles and their derivatives.

Recently we have reported a convenient method for the synthesis of condensed thiophenes from aryl propargyl sulfoxides.[2)] In its simplest form, this method involves successive [2, 3] and [3, 3] sigmatropic rearrangements of the phenyl propargyl sulfoxides (**1**) and subsequent ketalization(intramolecular addition of the thiol function on the carbonyl) giving the dihydrothiophenes (**2**), which are easily converted into the benzo[*b*]thiophenes (**3**) through the S_N2' attack of protic solvents (ethanol, water, acetic acid, *etc.*).



1 : R=H or CH_3



2 **3**

Chart 1

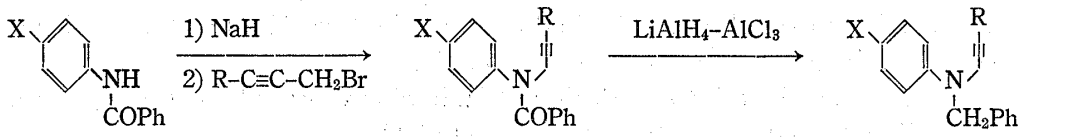
The ease with which the formation of the benzothiophenes could be accomplished prompted us to extend this reaction sequence to the nitrogen analogs. Thus, we have developed a new indole synthesis from N-propargylaniline N-oxides. In progress of our work, Thyagarajan, *et al.*[3)] reported the synthesis of 3-(*m*-chlorobenzoyloxymethyl)indoles by oxidation of N-propargylanilines with *m*-chloroperbenzoic acid and spontaneous further reactions on the basis of a similar concept.

1) Location: *Fukushima-ku, Osaka, 553, Japan.*
2) Y. Makisumi and S. Takada, *J. Chem. Soc., Chem. Comm.*, **1974**, 848.
3) B.S. Thyagarajan, J.B. Hillard, K.V. Reddy, and K.C. Majumdar, *Tetrahedron Letters*, **1974**, 1998; J.B. Hillard, K.V. Reddy, K.C. Majumdar, and B.S. Thyagarajan, *J. Heterocyclic Chem.*, **11**, 369 (1974).

The present paper deals with a general method for synthesizing 3-(substituted-methyl)-indoles (especially indole-3-acetonitriles) from N-propargylanilines in a one-pot reaction.

Formation and Rearrangements of N-Propargylaniline N-Oxides

The starting materials, N-benzyl-N-propargylanilines (5a—f), were prepared as follows. Successive treatment of benzanilides with sodium hydride and propargyl bromides yielded N-propargylbenzanilides (**4**), which were reduced with a 1:1 mixture of lithium aluminum hydride and aluminum chloride to afford **5** in good yields.



4

5a: R=CH_3, X=OCH_3
5b: R=CH_3, X=Cl
5c: R=CH_3, X=H
5d: R=H, X=OCH_3
5e: R=H, X=Cl
5f: R=H, X=H

Chart 2

When a solution of N-benzyl-N-(but-2-ynyl)-*p*-anisidine (**5a**) in deuteriochloroform was treated with one equivalent of *m*-chloroperbenzoic acid at room temperature for 10 min and then washed with aqueous sodium hydroxide at 0°, a solution of the very labile N-oxide (**6a**) was obtained without any significant contaminants; this was shown by its nuclear magnetic resonance (NMR) spectrum measured at −2.5°. In comparison of the NMR spectrum of **6a** with that of **5a**, the signals of protons adjacent to the nitrogen atom shifted to down field by 0.3—0.9 ppm in the spectrum of **6a**.

When the above solution of **6a** was allowed to stand at room temperature (25°) for 30 min, its NMR spectrum clearly showed that **6a** was quantitatively converted to the 3-methyl-ideneindoline (**7a**) (see the experimental section for the spectral assignment). This finding indicates that the conversion of **6a** to **7a** proceeds in very mild conditions and involves consecutive [2, 3] and [3, 3] sigmatropic rearrangements and accompanying ketalization (intramolecular addition of the amino function on the carbonyl) in a similar manner to that of the phenyl propargyl sulfoxides (**1**) to **2**.[2)]

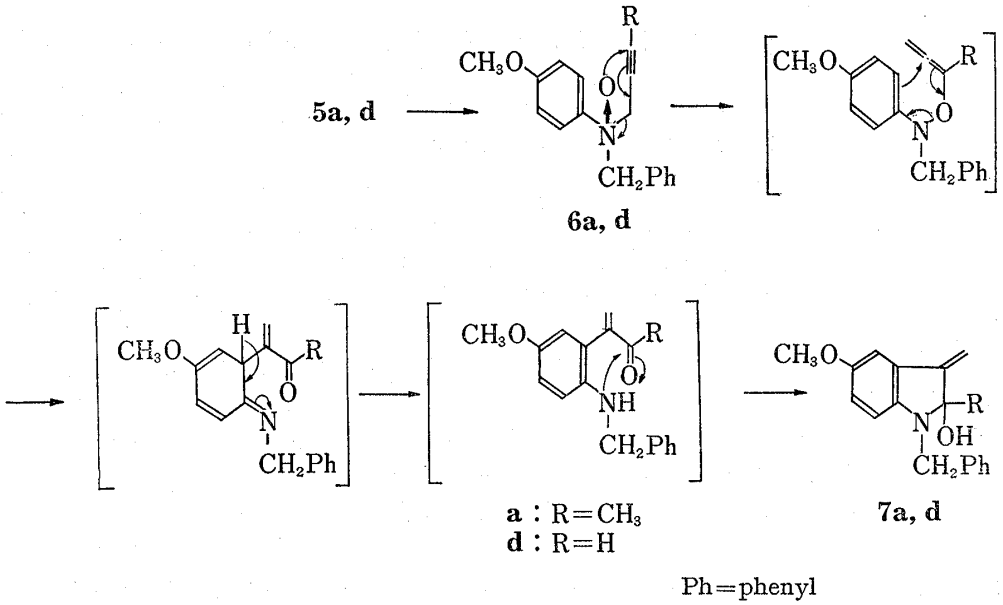


Chart 3

It is noteworthy that the N-oxides (**6**) were relatively stable in the reaction mixture in spite of their lability in neutral or basic media. (No significant changes were observed on the NMR spectra of the reaction mixtures within 1 hr at room temperature). This indicates that the initial [2, 3] rearrangement is suppressed by protonation on the oxygen atom of the N-oxide function with *m*-chlorobenzoic acid present in the reaction mixture.

Formation of an Indole Ring

Structural similarity of the indolines (**7**) to the dihydrobenzothiophenes (**2**) suggests that **7** may be converted to the indoles by addition of a nucleophilic reagent through an S_N2' reaction of the allylic hydroxyl group or through elimination of the hydroxyl group (the indolenine-type intermediates) and conjugate addition of the nucleophile.

When thiophenol was added into a solution of **7a** in chloroform at room temperature, the 3-phenylthiomethylindole (**8a**) was obtained in a good yield.

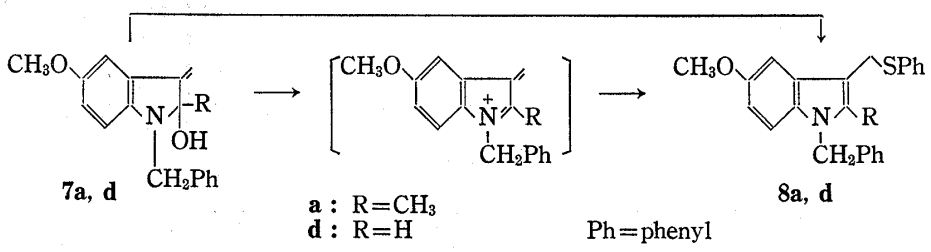


Chart 4

In the case of N-benzyl-N-(prop-2-ynyl)-*p*-anisidine N-oxide (**6d**), the indoline intermediate corresponding to **7a** could not be detected by NMR spectroscopy. However, treatment of **6d** with thiophenol gave the phenylthiomethylindole (**8d**) in 32% yield based on the starting aniline (**5d**). This result indicates the existence of the indoline intermediate (**7d**) (or its equivalent) having a short life-time.

The success of this process suggests that a variety of 3-(substituted-methyl)indoles could be synthesized by treatment of the N-propargylaniline N-oxides with appropriate nucleophiles.

Formation of Indole-3-acetonitriles

The use of potassium cyanide as a nucleophilic reagent in the above process should afford indole-3-acetonitriles which are useful synthetic intermediates in the indole chemistry. To simplify the laboratory procedure, a method without isolation of the unstable N-oxides (**6**) and indolines (**7**) was developed.

An N-benzyl-N-(but-2-ynyl)aniline (**5**) (R=CH_3) was oxidized with one equivalent of *m*-chloroperbenzoic acid in methylene chloride and then the solvent was replaced with N,N-dimethylformamide[4] at 0°. Treatment of this mixture with an aqueous solution of excess potassium cyanide at 50° for 30 min gave a 2-methylindole-3-acetonitrile **9** in 50—70% yield.

The use of an N-(prop-2-ynyl)aniline (**5**) (R=H) as a starting material gave an indole-3-acetonitrile (**9**) in *ca.* 30% yield and a 2-cyano-3-methylindole (**10**) in 7—9% yield. Formation of the latter compound was suggested to involve a nucleophilic addition of cyanide ion on the 2-position of the methylideneindolenine intermediate and subsequent hydrogen transfer as shown in Chart 5.

In this one-pot procedure, no *m*-chlorobenzoyloxymethylindole was formed, although *m*-chlorobenzoic acid present in the reaction mixture is able to serve as a nucleophile. Presumably this fact depends on that cyanide ion is more nucleophilic than *m*-chlorobenzoate ion. Since the reaction mixture became alkaline by addition of potassium cyanide, the rearrangements of the N-oxides must have been accelerated as described before.

4) A considerable amount of the starting aniline was recovered when N,N-dimethylformamide was used as a solvent in oxidation.

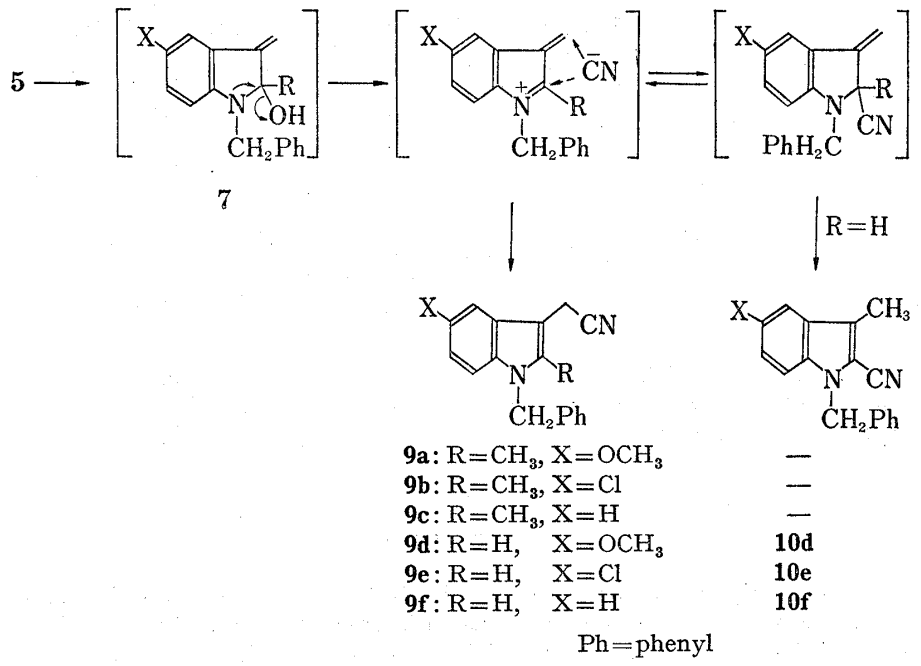


Chart 5

The acetonitriles (**9**) prepared above can be used as key synthetic intermediates in the indole chemistry. For instance, hydrolysis of 1-benzyl-5-methoxy-2-methylindole-3-acetonitrile (**9a**) with potassium hydroxide in aqueous ethanol gave the indole-3-acetic acid (**11**),[5] which was debenzylated with sodium-liquid ammonia, giving 5-methoxy-2-methylindole-3-acetic acid (**12**)[5] in good overall yield. The acid (**12**) can be converted into the anti-inflammatory agent indomethacin in the known method.[6]

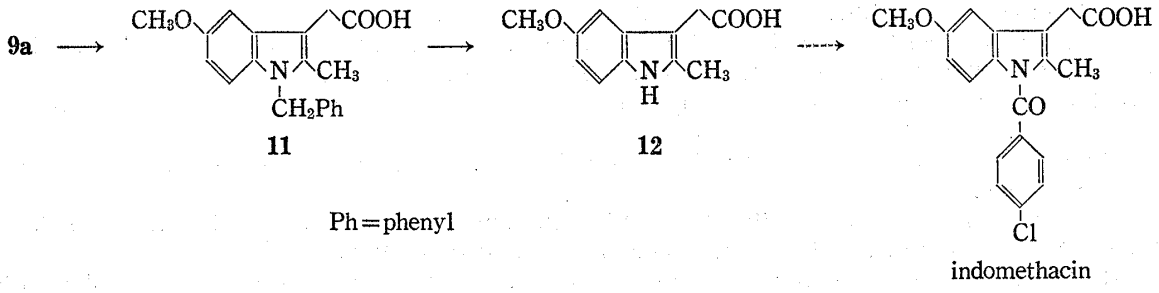


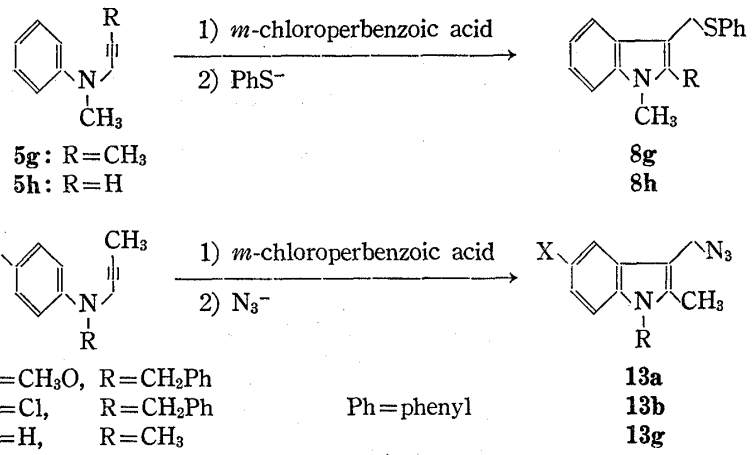
Chart 6

Formation of 3-Phenylthiomethylindoles and 3-Azidomethylindoles

The one-pot synthesis of indole-3-acetonitriles described above was applicable to that of 3-phenylthiomethylindoles (**8**) or 3-azidomethylindoles (**13**) by simply using sodium phenylmercaptide or sodium azide, respectively, as a nucleophilic reagent. Chart 7 shows the indoles (**8** and **13**) obtained from N-propargylanilines in this procedure. The 3-azidomethylindoles (**13**) can be converted to the 3-aminomethylindoles (**14**) on catalytic hydrogenation with palladium on carbon.

In summary, the indole-3-acetonitriles and other 3-(substituted-methyl)indoles were prepared from N-propargylanilines under mild conditions in a one-pot reaction. This process provides a simple, general synthesis of these kinds of indoles and their derivatives.

5) E. Shaw, *J. Am. Chem. Soc.*, **77**, 4319 (1955).
6) T.Y. Shen, R.L. Ellis, T.B. Windholz, A.R. Matzuk, A. Rosegay, S. Lucas, B.E. Witzel, C.M. Stammer, A.N. Wilson, F.W. Holly, J.P. Willett, L.H. Sarett, W.J. Holtz, E.A. Risley, G.W. Nuss, and C.A. Winter, *J. Am. Chem. Soc.*, **85**, 488 (1963).



5g: R=CH_3 **8g**
5h: R=H **8h**

5a: X=CH_3O, R=CH_2Ph **13a**
5b: X=Cl, R=CH_2Ph Ph=phenyl **13b**
5g: X=H, R=CH_3 **13g**

Chart 7

Experimental

Boiling points and melting points are uncorrected. NMR spectra were recorded on a Varian A-60 or T-60 spectrometer using tetramethyl silane (TMS) as an internal standard. Infrared (IR) spectra were recorded on a Jasco IRA-I spectrometer. Commercial *m*-chloroperbenzoic acid was used after its purity was determined by iodometric titration.

Preparation of N-Propargylbenzanilides (4a—f)——General Procedure: A solution of a benzanilide (0.02 mole) in dimethyl formamide (DMF) (30 ml) was added into a stirred suspension of NaH (1.15 g, *ca.* 0.024 mole as a 50% oil dispersion; washed with dry pentane before use) in DMF at 60° over a 20 min period under nitrogen. The mixture was stirred at 60° until hydrogen evolution ceased, and then cooled to 0°. To this mixture was added a solution of but-2-ynyl bromide or prop-2-ynyl bromide (0.022 mole) in DMF (4 ml) at 0—5° with stirring. After the mixture was stirred at 0—5° for 1.5 hr, iced water was added and the mixture was extracted with ether. The extract was washed with water, dried over Na_2SO_4, and evaporated. The solid residue was purified by recrystallization.

N-(But-2-ynyl)benzo-*p*-aniside (**4a**): Yield 74%, mp 85—86° (from EtOH). *Anal.* Calcd. for $C_{18}H_{17}O_2N$: C, 77.39; H, 6.13; N, 5.01. Found: C, 77.10; H, 6.07; N, 4.82.

N-(But-2-ynyl)benzo-*p*-chloroanilide (**4b**): Yield 88%, mp 102—104° (from EtOH). *Anal.* Calcd. for $C_{17}H_{14}ONCl$: C, 71.96; H, 4.97; N, 4.94. Found: C, 71.98; H, 4.73; N, 5.03.

N-(But-2-ynyl)benzanilide (**4c**): The oily residue (*ca.* 95% yield) was used in the next step without further purification.

N-(Prop-2-ynyl)benzo-*p*-aniside (**4d**): The oily residue (*ca.* 95% yield) was used in the next step without further purification.

N-(Prop-2-ynyl)benzo-*p*-chloroanilide (**4e**): Yield 88%, mp 65—66° (from ether–hexane). *Anal.* Calcd. for $C_{16}H_{12}ONCl$: C, 71.25; H, 4.48; N, 5.19. Found: C, 71.45; H, 4.50; N, 5.05.

N-(Prop-2-ynyl)benzanilide (**4f**): The oily residue (*ca.* 95% yield) was used in the next step without further purification.

Preparation of N-Benzyl-N-propargylanilines (5a—f) by Reduction of Benzanilides (4a—f)——General Procedure: Powdered $AlCl_3$ (2.66 g, 0.02 mole) was added into a stirred suspension of $LiAlH_4$ (760 mg, 0.02 mole) in anhydrous ether (60 ml) at ice-bath temperature. To this mixture was added a solution of a benzanilide (0.01 mole) in anhydrous ether (120 ml) at 0° over a 30 min period. After the mixture was stirred at room temperature for 1.5 hr, the excess reagent was carefully decomposed by iced water at 0° and then a cold aqueous solution of NaOH (2.4 g/water 30 ml) was added at 0°. The organic layer was separated and the aqueous phase was extracted with ether. The combined organic solutions were washed with water, dried over Na_2SO_4, and evaporated. The residue was purified by recrystallization (for the solid residue) or by chromatography on silica gel (for the oily residue).

N-Benzyl-N-(but-2-ynyl)-*p*-anisidine (**5a**): Yield 94%, mp 47—48° (from EtOH). NMR ($CDCl_3$) δ: 1.78 (3H, t, $-C\equiv C-CH_3$), 3.73 (3H, s, OCH_3), 3.84 (2H, q, $-CH_2-C\equiv C-$), 4.40 (2H, s, $-C\underline{H}_2-C_6H_5$), 6.84 (4H, s, aromatic protons), 7.27 (5H, s, $-CH_2-C_6\underline{H}_5$). *Anal.* Calcd. for $C_{18}H_{19}ON$: C, 81.47; N, 7.22; N, 5.28. Found: C, 81.38; H, 7.48; N, 5.55.

N-Benzyl-N-(but-2-ynyl)-*p*-chloroaniline (**5b**): Yield 91%, a colorless oil. *Anal.* Calcd. for $C_{17}H_{16}NCl$: C, 75.68; H, 5.98; N, 5.19. Found: C, 75.67; H, 5.90; N, 5.22.

N-Benzyl-N-(but-2-ynyl)aniline (**5c**): Yield 90%, a colorless oil. *Anal.* Calcd. for $C_{17}H_{17}N$: C, 86.77; H, 7.28; N, 5.95. Found: C, 86.47; H, 7.22; N, 6.01.

N-Benzyl-N-(prop-2-ynyl)-*p*-anisidine (**5d**): Yield 92%, mp 67—68° (from EtOH). NMR ($CDCl_3$) δ: 2.20 (1H, t, $-C\equiv C-H$), 3.75 (3H, s, OCH_3), 3.88 (2H, d, $-CH_2-C\equiv C-$), 4.40 (2H, s, $-C\underline{H}_2-C_6H_5$), 6.84 (4H, s,

aromatic protons), 7.30 (5H, s, $-CH_2-C_6\underline{H}_5$). *Anal.* Calcd. for $C_{17}H_{17}ON$: C, 81.24; H, 6.82; N, 5.57. Found: C, 81.02; H, 6.99; N, 5.82.

N-Benzyl-N-(prop-2-ynyl)-*p*-chloroaniline (**5e**): Yield 95%, a colorless oil. *Anal.* Calcd. for $C_{16}H_{14}NCl$: C, 75.14; H, 5.52; N, 5.48. Found: C, 75.16; H, 5.51; N, 5.26.

N-Benzyl-N-(prop-2-ynyl)aniline (**5f**): Yield 90%, mp 44—45° (from EtOH). *Anal.* Calcd. for $C_{16}H_{15}N$: C, 86.84; H, 6.83; N, 6.33. Found: C, 87.03; H, 6.66; N, 6.49.

N-Methyl-N-(but-2-ynyl)aniline (5g)——A solution of N-methylaniline (31.45 g, 0.293 mole) and but-2-ynyl bromide (19.4 g, 0.146 mole) in benzene (100 ml) was refluxed for 5 hr. After addition of aqueous NaOH to the cooled solution, the mixture was extracted with ether. The extract was washed with water, and dried over Na_2SO_4. The solution was concentrated under an atmospheric pressure and then distilled *in vacuo*, giving 20.2 g (87%) of **5g** as a colorless oil, bp 93—95° (0.45 mmHg), *Anal.* Calcd. for $C_{11}H_{13}N$: C, 82.97; H, 8.23; N, 8.80. Found: C, 82.75; H, 8.08; N, 9.01.

N-Methyl-N-(prop-2-ynyl)aniline (5h)——A solution of N-methylaniline (21.4 g, 0.2 mole) and prop-2-ynyl bromide (11.9 g, 0.1 mole) in benzene (100 ml) was refluxed for 5 hr. Work-up as described for **5g** gave 12.5 g (86%) of **5h** as a colorless oil, bp 105—106° (10 mmHg), solidified in a refrigerator, *Anal.* Calcd. for $C_{10}H_{11}N$: C, 82.71; H, 7.64; N, 9.65. Found: C, 82.59; H, 7.69; N, 9.62.

Formation of the N-Oxide 6a from the Aniline (5a)——The aniline **5a** (133 mg, 0.5 mmole) was dissolved in $CDCl_3$ and then *m*-chloroperbenzoic acid (84% purity, 103 mg, 1 eq) was added at 0°. The mixture was stirred for 10 min at room temperature and then cooled to 0°. The mixture was washed with cold 5% aqueous NaOH and cold saturated NaCl and dried over molecular sieves 4A, while the temperature was maintained below 5°. Within 30 min, the NMR spectrum of the cold solution was measured at −2.5°. NMR ($CDCl_3$) δ: 1.92 (3H, t, $-C\equiv C-CH_3$), 3.82 (3H, s, OCH_3), 4.18 (2H, q, $-CH_2-C\equiv C-$), 4.80 (2H, AB-q, $J_{AB}=12.0$, $N-C\underline{H}_2-C_6H_5$), 6.87 (2H, d, protons *ortho* to OCH_3), 7.77 (2H, d, protons *meta* to OCH_3), 7.35 (5H, s, phenyl protons).

Formation of the N-Oxide 6d from the Aniline (5d)——The $CDCl_3$ solution of **6d** was obtained from **5d** by the procedure identical with that described for **6a**. Its NMR spectrum measured at −2.5° showed formation of the N-oxide (**6d**) without significant contaminations: NMR ($CDCl_3$) δ: 2.66 (1H, t, $-C\equiv C-H$), 3.84 (3H, s, OCH_3), 4.28 (2H, d, $-CH_2-C\equiv C-$), 4.83 (2H, AB-q, $J_{AB}=12.0$, $-C\underline{H}_2-C_6H_5$), 6.89 (2H, d, protons *ortho* to OCH_3), 7.78 (2H, d, protons *meta* to OCH_3), 7.36 (5H, s, phenyl protons).

Formation of the Indoline 7a from the N-Oxide (6a)——The solution of the N-oxide (**6a**) in $CDCl_3$ prepared as described above was warmed at 25° for 30 min. The NMR spectrum measured at −2.5° showed almost quantitative formation of the indoline **7a**. NMR ($CDCl_3$) δ: 1.54 (3H, s, $C-CH_3$), 3.27 (1H, br s, OH), 3.72 (3H, s, OCH_3), 4.43 (2H, AB-q, $J_{AB}=17.0$, $-C\underline{H}_2-C_6H_5$), 5.37 and 5.55 (1H each, s, vinyl protons), 6.10 (1H, d, $J=8.5$, C-7 proton), 6.65 (1H, dd, $J=2.5$ and 8.5, C-6 proton), 6.95 (1H, d, $J=2.5$, C-4 proton), 7.37 (5H, s, phenyl protons).

1-Benzyl-5-methoxy-2-methyl-3-phenylthiomethylindole (8a)——Into a stirred solution of the anisidine (**5a**) (1.167 g, 4.4 mmoles) in $CHCl_3$ (10 ml) was added *m*-chloroperbenzoic acid (84% purity, 990 mg, 1.1 eq) at 0°, and then warmed at room temperature for 10 min. After the mixture was cooled again to 0°, cold 10% aqueous NaOH (4 ml) was added with vigorous stirring, while the temperature was maintained below 5°. The organic layer was separated, washed with cold saturated NaCl (5 ml), and dried over molecular sieves 4A at ice-bath temperature. After the solution was warmed to room temperature and allowed to stand for 30 min, thiophenol (1 g, *ca.* 2 eq) was added and the mixture was stirred at room temperature for 2 hr. The solution was diluted with $CHCl_3$, washed with aqueous NaOH, water and saturated NaCl, and dried over Na_2SO_4. Removal of the solvent gave 1.41 g of the residue, which was chromatographed on silica gel with benzene–hexane (1: 1) to afford 680 mg (42%) of **8a**, mp 128—130° (from EtOH). NMR ($CDCl_3$) δ: 2.08 (3H, s, $C-CH_3$), 3.82 (3H, s, OCH_3) 4.27 (2H, s, $-C\underline{H}_2-SC_6H_5$), 5.18 (2H, s, $-C\underline{H}_2-C_6H_5$), 6.9—7.5 (13H, m, aromatic protons). *Anal.* Calcd. for $C_{24}H_{23}ONS$: C, 77.17; H, 6.21; N, 3.75; S, 8.59. Found: C, 77.41; H, 5.97; N, 3.89; S, 8.89.

1-Benzyl-5-methoxy-3-phenylthiomethylindole (8d)——The indole (**8d**) was obtained from the anisidine (**5d**) according to the procedure for **8a** with some modifications. Oxidation and work-up as described for **8a** gave a cold solution of the N-oxide (**6d**). Before this solution was warmed up to room temperature, thipohenol was added at 0° and then the solution was stirred at room temperature for 1 hr. From here on, work-up was carried out as described for **8a**. Chromatography using silica gel and benzene–hexane (1: 1) gave a 32% yield of **8d**, mp 77—78° (from EtOH). NMR ($CDCl_3$) δ: 3.82 (3H, s, OCH_3), 4.28 (2H, s, $-C\underline{H}_2SC_6H_5$), 5.17 (2H, s, $-C\underline{H}_2-C_6H_5$), 6.8—7.4 (14H, m, aromatic protons). *Anal.* Calcd. for $C_{23}H_{21}ONS$: C, 76.85; H, 5.89; N, 3.90; S, 8.92. Found: C, 77.06; H, 5.70; N, 3.67; S, 8.91.

Formation of Indole-3-acetonitriles (9a—f) and 2-Cyano-3-methylindoles (10d—f) from Anilines (5a—f)——General Procedure: *m*-Chloroperbenzoic acid (1 mmole) was added into a solution of an aniline (1 mmole) in CH_2Cl_2 (2 ml) at 0°. The mixture was stirred at room temperature for 10 min and cooled again to 0°. The mixture was evaporated at 0° *in vacuo* and the residue was dissolved in cold DMF (8 ml). To this solution was added an aqueous solution of KCN (390 mg, 6 mmole/water 2 ml) and the mixture was stirred at 50° for 30 min, then diluted with water, and extracted with ether. The extract was washed with water, dried over Na_2SO_4, and evaporated. The residue was chromatographed on silica gel.

1-Benzyl-5-methoxy-2-methylindole-3-acetonitrile (**9a**): Yield 67%, mp 132—134° (from benzene–ether), IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2250 (CN), NMR ($CDCl_3$) δ: 2.30 (3H, s, C–CH_3), 3.77 (2H, s, –CH_2CN), 3.85 (3H, s, OCH_3), 5.21 (2H, s, N–$C\underline{H}_2$–C_6H_5). *Anal.* Calcd. for $C_{19}H_{18}ON_2$: C, 78.59; H, 6.25; N, 9.65. Found: C, 78.83: H, 6.18; N, 9.93.

1-Benzyl-5-chloro-2-methylindole-3-acetonitrile (**9b**): Yield 54%, mp 175—177° (from EtOH), IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2250 (CN), NMR ($CDCl_3$) δ: 2.32 (3H, s, C–CH_3), 3.70 (2H, s, –CH_2CN), 5.22 (2H, s, N–$C\underline{H}_2$–C_6H_5). *Anal.* Calcd. for $C_{18}H_{15}N_2Cl$: C, 73.34; H, 5.13; N, 9.50. Found: C, 73.44; H, 5.10; N, 9.46.

1-Benzyl-2-methylindole-3-acetonitrile (**9c**): Yield 62%, mp 112—114° (from benzene–ether). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2250 (CN), NMR ($CDCl_3$) δ: 2.32 (3H, s, C–CH_3), 3.75 (2H, s, –CH_2CN), 5.25 (2H, s, N–$C\underline{H}_2$–C_6H_5). *Anal.* Calcd. for $C_{18}H_{16}N_2$: C. 83.04; H, 6.20; N, 10.76. Found: C, 83.22; H, 6.23; N, 10.57.

1-Benzyl-5-methoxyindole-3-acetonitrile (**9d**): Yield 29%, mp 79—81° (from EtOH), IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2250 (CN), NMR ($CDCl_3$) δ: 3.73 (2H, s, –CH_2CN), 3.54 (3H, s, OCH_3), 5.18 (2H, s, N–$C\underline{H}_2$–C_6H_5). *Anal.* Calcd. for $C_{18}H_{16}ON_2$: C, 78.23; H, 5.84; N, 10.14. Found: C, 78.10; H, 5.78; N, 10.12.

1-Benzyl-2-cyano-5-methoxy-3-methylindole (**10d**): Yield 9%, mp 106—107° (from EtOH), IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2220 (CN), NMR ($CDCl_3$) δ: 2.45 (3H, s, C–CH_3), 3.84 (3H, s, OCH_3), 5.35 (2H, s, N–$C\underline{H}_2$–C_6H_5). *Anal.* Calcd. for $C_{18}H_{16}ON_2$: C, 78.23; H, 5.84; N, 10.14. Found: C, 78.45; H, 5.64; N, 10.07.

1-Benzyl-5-chloroindole-3-acetonitrile (**9e**): Yield 32%, mp 123—124° (from EtOH), IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2250 (CN), NMR ($CDCl_3$) δ: 3.75 (2H, s, –CH_2CN), 5.25 (2H, s, N–$C\underline{H}_2$–C_6H_5). *Anal.* Calcd. for $C_{17}H_{13}N_2Cl$: C, 72.73; H, 4.67; N, 9.98. Found: C, 72.70; H, 4.82; N, 9.80.

1-Benzyl-5-chloro-2-cyano-3-methylindole (**10e**): Yield 7%, mp 133—134° (from EtOH), IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2220 (CN), NMR ($CDCl_3$) δ: 2.50 (3H, s, C–CH_3), 5.43 (2H, s, N–$C\underline{H}_2$–C_6H_5). *Anal.* Calcd. for $C_{17}H_{13}N_2Cl$: C, 72.73; H, 4.67; N, 9.98. Found: C, 72.96; H, 4.82; N, 9.77.

1-Benzylindole-3-acetonitrile (**9f**): Yield 28%, mp 95—96° (from EtOH), IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2250 (CN), NMR ($CDCl_3$) δ: 3.80 (2H, s, –CH_2CN), 5.25 (2H, s, N–$C\underline{H}_2$–C_6H_5). *Anal.* Calcd. for $C_{17}H_{14}N_2$: C, 82.90; H, 5.73; N, 11.37. Found: C, 82.71; H, 5.46; N, 11.36.

1-Benzyl-2-cyano-3-methylindole (**10f**): Yield 9%, mp 69.5—70.5° (from MeOH), IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2220 (CN), NMR ($CDCl_3$) δ: 2.48 (3H, s, C–CH_3), 5.33 (2H, s, N–$C\underline{H}_2$–C_6H_5). *Anal.* Calcd. for $C_{17}H_{14}N_2$: C, 82.90; H, 5.73; N, 11.37. Found: C, 83.05; H, 5.95; N, 11.50.

1-Benzyl-5-methoxy-2-methylindole-3-acetic Acid (11)——To a solution of the acetonitrile **9a** (580 mg, 2 mmoles) in EtOH (30 ml) was added an aqueous solution of KOH (1.5 g, 27 mmoles/water 6 ml). The mixture was refluxed for 45 hr under nitrogen and concentrated to *ca.* 10 ml *in vacuo*. After addition of water, the mixture was extracted with ether in order to remove basic or neutral materials. The aqueous phase was acidified (pH *ca.* 2) with 2N HCl and extracted with benzene. The extract was washed with water and dried over Na_2SO_4. Evaporation of the solvent gave a solid residue (574 mg), which was recrystallized from EtOH to afford 540 mg (87%) of **11**, mp 179—182° (lit.[5] mp 174—175°). IR $\nu_{max}^{CHCl_3}$: 1720 (COOH). *Anal.* Calcd. for $C_{19}H_{19}O_3N$: C, 73.76; H, 6.19; N, 4.53. Found: C, 73.87; H, 6.26; N, 4.54.

5-Methoxy-2-methylindole-3-acetic Acid (12)——To a suspension of the acetic acid (**11**) (300 mg, 0.97 mmole, powdered) in liq. NH_3 (60 ml) were added small pieces of metallic Na over a 2 hr period under nitrogen until a permanent deep blue color was obtained. This required *ca.* 100 mg of Na. After addition of NH_4Cl (300 mg), NH_3 was evaporated and the residue was dissolved in water. The solution was acidified with 2N HCl and extracted with ethyl acetate. The extract was washed with saturated NaCl and dried over Na_2SO_4. Removal of the solvent gave a solid residue (202 mg), which was recrystallized from EtOH–benzene to afford 174 mg (82%) of **12**, mp 164—166° (lit.[5] mp 161—162°). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3560 (NH), 1720 (COOH). *Anal.* Calcd. for $C_{12}H_{13}O_3N$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.83; H, 6.19; N, 6.19.

1,2-Dimethyl-3-phenylthiomethylindole (8g)——Into a stirred solution of the aniline **5g** (1.59 g, 0.01 mole) in CH_2Cl_2 (20 ml) was added *m*-chloroperbenzoic acid (78.4% purity, 2.20 g, 1 eq) at 0°. The mixture was stirred at room temperature for 10 min and cooled to 0°. The solvent was removed completely at 0° *in vacuo* and the residue was dissolved in cold DMF (40 ml). To this solution was added a solution of thiophenol (4.7 ml, *ca.* 5 eq) and NaOH (2 g, 0.05 mole) in water (10 ml) at 0° under nitrogen and the mixture was stirred at 50° for 30 min. After addition of water, the mixture was extracted with ether. The extract was washed with 5% aqueous NaOH, water and saturated NaCl, and dried over Na_2SO_4. After removal of the solvent, the solid residue (*ca.* 3 g) was recrystallized from EtOH giving 1.36 g (51%) of **8g**, mp 106—108°. NMR ($CDCl_3$) δ: 2.22 (3H, s, C–CH_3), 3.58 (3H, s, N–CH_3), 4.30 (2H, s, –$C\underline{H}_2$–SC_6H_5), 7.0—7.6 (9H, m, aromatic protons). *Anal.* Calcd. for $C_{17}H_{17}NS$: C, 76.36; H, 6.41; N, 5.24; S, 11.99. Found: C, 76.66; H, 6.45; N, 5.26; S, 12.23.

1-Methyl-3-phenylthiomethylindole (8h)——The indole **8h** was obtained from **5h** according to the procedure described for **8g**. Chromatography of the residue on basic alumina gave a 32% yield of **8h**, mp 92—93° (from EtOH). NMR ($CDCl_3$) δ: 3.60 (3H, s, N–CH_3), 4.27 (2H, s, –$C\underline{H}_2$–S–C_6H_5), 6.77 (1H, s, C-2 proton), 6.85—7.65 (9H, m, aromatic protons). *Anal.* Calcd. for $C_{16}H_{15}NS$: C, 75.85; H, 5.97; N, 5.53; S, 12.66. Found: C, 75.96; H, 5.92; N, 5.60; S, 12.89.

Formation of 3-Azidomethylindoles (13a, b, g) from Anilines (5a, b, g)——General Procedure: *m*-Chloroperbenzoic acid (1 mmole) was added into a solution of an aniline (1 mmole) in CH_2Cl_2 (2 ml) at 0°. The mix-

ture was stirred at room temperature for 10 min and cooled to 0°. The solvent was evaporated at 0° *in vacuo* and the residue was dissolved in cold DMF (4 ml). To this solution was added an aqueous solution of NaN_3 (325 mg, 5 mmoles/water 1 ml) and the mixture was stirred at 50° for 30 min. After dilution with water, the mixture was washed with aqueous $NaHCO_3$ and water, and dried over Na_2SO_4. Removal of the solvent gave a solid residue, which was recrystallized at low temperature.

3-Azidomethyl-1-benzyl-5-methoxy-2-methylindole (**13a**): Yield 51%, mp 84—85° (from benzene–hexane), IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2100 (N_3), NMR ($CDCl_3$) δ: 2.34 (3H, s, C–CH_3), 3.85 (3H, s, OCH_3), 4.48 (2H, s, –CH_2–N_3), 5.25 (2H, s, N–$C\underline{H}_2$–C_6H_5). *Anal.* Calcd. for $C_{18}H_{18}ON$: C, 70.56; H, 5.92; N, 18.29. Found: C, 70.73; H, 5.87; N, 18.08.

3-Azidomethyl-1-benzyl-5-chloro-2-methylindole (**13b**): Yield 71%, mp 106—108°, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2100 (N_3), NMR ($CDCl_3$) δ: 2.35 (3H, s, C–CH_3), 4.45 (2H, s, –CH_2–N_3), 5.25 (2H, s, N–$C\underline{H}_2$–C_6H_5). *Anal.* Calcd. for $C_{17}H_{15}N_4Cl$: C, 65.70; H, 4.87; N, 18.03. Found: C, 65.86; H, 4.93; N, 17.83.

3-Azidomethyl-1,2-dimethylindole (**13g**): Yield 45%, mp 60—62° (from EtOH), IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2100 (N_3), NMR ($CDCl_3$) δ: 2.42 (3H, s, C–CH_3), 3.65 (3H, s, N–CH_3), 4.50 (2H, s, –CH_2N_3). *Anal.* Calcd. for $C_{11}H_{12}N_4$: C, 65.98; H, 6.04; N, 27.98. Found: C, 65.77; H, 5.87; N, 27.79.

3-Aminomethyl-1,2-dimethylindole (14g)——The indole (**13g**) (300 mg) was hydrogenated with 5% Pd-C (100 mg) in EtOH (15 ml) at room temperature under an atmospheric pressure for 4 hr. The catalyst was filtered and the filtrate was evaporated giving an oil (245 mg) of **14g**. NMR ($CDCl_3$) δ: 1.93 (2H, s, NH_2), 2.37 (3H, s, C–CH_3), 3.58 (3H, s, N–CH_3), 3.92 (2H, s, –$C\underline{H}_2$–NH_2), 6.9—7.1 and 7.4—7.6 (3H and 1H, respectively, m, aromatic protons). This oil was dissolved in EtOH, and a saturated solution of picric acid in EtOH was added. The resulting crystals were filtered and recrystallized from DMF–EtOH giving 330 mg (67%) of the picrate, mp 138—146° (decomp.). *Anal.* Calcd. for $C_{17}H_{17}O_7N_5$: C, 50.62; H, 4.25; N, 17.36. Found: C, 50.57; H, 4.30; N, 17.29.