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# Preparation of 3-Arylindoles

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During the course of our studies on the reactivity of indoles, various 3-arylindoles were required as substrates. Though 3-phenylindole (**1a**) has been prepared by Fischer,[2] *p*-substituted derivatives are scarecely known. We now report the preparation of some *p*-substituted 3-phenylindoles (**1b—h**).

For the preparation of 3-(*p*-methoxyphenyl)- and 3-(*p*-bromophenyl)indoles (**1b** and **1d**), we have chosen the Fischer indolization of arylacetaldehyde. *p*-Methoxyphenylacetaldehyde (**5a**) was prepared from *p*-anisaldehyde *via* the glicidic ester (**3a**) following Ban's procedure.[3]

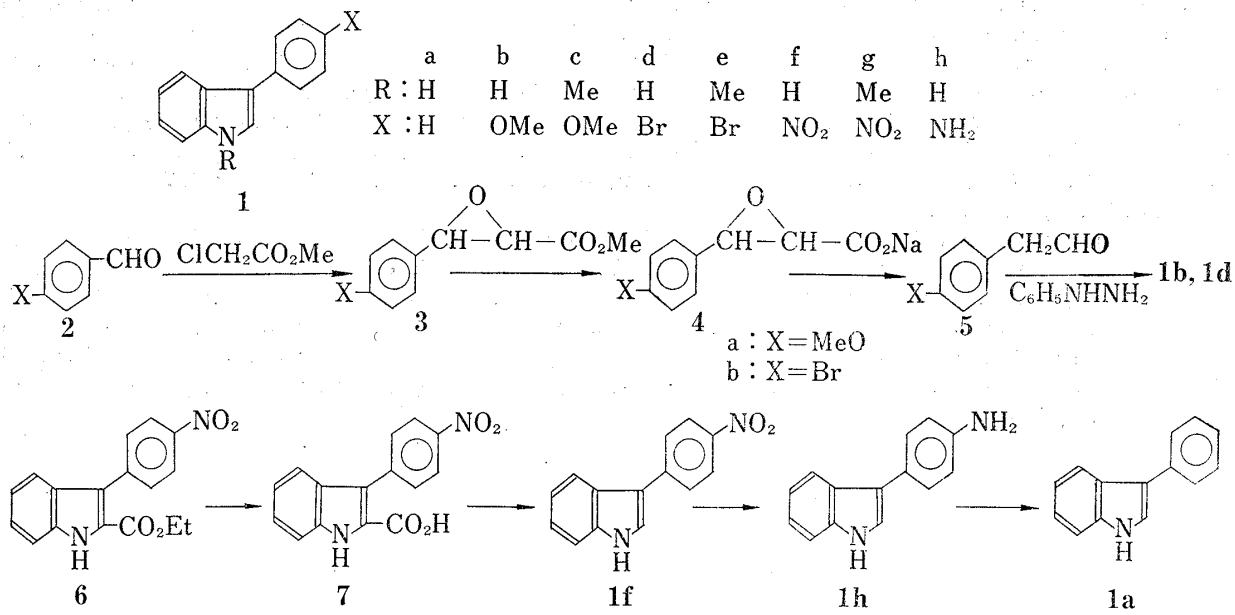


Chart 1

The Darzens reaction of *p*-bromobenzaldehyde under the similar condition did not give satisfactory yield of the glycidic ester (**3b**). However, the glycidic ester (**3b**) was obtained in 80% yield when more than two moles of methyl chloroacetate and sodium methoxide were used.[4] A minor difference was also observsd in the decarboxylation of the glycidic acid. Decarboxylation of sodium glycidate (**4a**) was completed in refluxing benzene by the addition of acetic acid. Under the similar reaction condition, **4b** was not decarboxylated, and heating of its free acid in xylene gave the *p*-bromophenylacetaldehyde (**5b**). The arylacetaldehydes, **5a** and **5b**, were identified as the semicarbazone[5] or 2,4-dinitrophenylhydrazone.[6]

1) Location: *Yayoi-cho, Chiba-shi, 280, Japan.*
2) E. Fischer and T. Schmidt, *Ber.*, **21**, 1072, 1811 (1881).
3) Y. Ban and T. Ohishi, *Chem. Pharm. Bull.* (Tokyo), **6**, 574 (1958).
4) H. Kugita, H. Inoue, M. Ikezaki, and S. Takeo, *Chem. Pharm. Bull.* (Tokyo), **18**, 2028 (1970).
5) H. Plieninger, Ger. Pat., 957029 [*Chem. Abst.*, **53**, 18870h (1959)].
6) V.M. Naidan, N.V. Dzumedzei, and A.D. Domchrovskii, *Zh. Organ. Khim.*, **1**, 1377 (1965), [*Chem. Abst.*, **64**, 721 (1966)].

The Fischer indolyzation of the phenylhydrazones of these aldehyde with boron trifluoride in acetic acid[7] gave the corresponding 3-arylindole (**1b** and **1d**) in 40—50% yield. 3-(*p*-Nitrophenyl)indole (**1f**) was prepared by the decarboxylation of the 2-ethoxycarbonyl-3-*p*-nitrophenylindole (**6**)[8] which had been prepared from ethyl *p*-nitrophenylpyruvate. Heating of 2-carboxy-3-(*p*-nitrophenyl)indole (**7**) in quinoline with catalytic amount of copper salt of 7 gave 90% of the indole (**1f**).[9] The reduction of the *p*-nitro group in **1f** with Fe–HCl gave 3-(*p*-aminophenyl)indole (**1h**). The reduction of the diazonium salt of **1h** with hypophosphorous acid provided **1a**.

N-Methyl derivatives of these 3-arylindoles were obtained by the methylation in liquid ammonia with sodium amide and methyl iodide. N-Methylation of **1f** in this procedure gave poor yield of **1g**, but gave **1g** in 85% yield by heating of **1f** with potassium carbonate and methyl iodide in acetone.

The analytical and the ultraviolet spectral data of these indoles are shown in Table I and II.

Table I. Analytical Data of 3-Arylindoles

| Compound No. | R | X | mp (C°) | Mol. formula | Analysis (%) Calcd. C | H | N | Found. C | H | N |
|---|---|---|---|---|---|---|---|---|---|---|
| **1b** | H | OMe | 132—134 | $C_{15}H_{13}ON$ | 80.69 | 5.87 | 6.27 | 80.51 | 5.77 | 6.54 |
| **1c** | Me | OMe | 107—109 | $C_{16}H_{15}ON$ | 80.98 | 6.37 | 5.90 | 80.79 | 6.16 | 6.12 |
| **1d** | H | Br | 141—143 | $C_{14}H_{10}NBr$[a] | 61.76 | 3.68 | 5.15 | 61.91 | 3.80 | 5.07 |
| **1e** | Me | Br | 92— 94 | $C_{15}H_{12}NBr$[b] | 62.94 | 4.20 | 4.83 | 62.65 | 4.13 | 4.96 |
| **1f** | H | $NO_2$ | 168—171 | $C_{14}H_{10}O_2N_2$ | 70.58 | 4.23 | 11.76 | 69.97 | 4.20 | 11.64 |
| **1g** | Me | $NO_2$ | 153—155 | $C_{15}H_{12}O_2N_2$ | 71.41 | 4.80 | 11.11 | 71.30 | 4.79 | 11.13 |
| **1h** | H | $NH_2$ | 159—161 | $C_{14}H_{12}N_2$ | 80.74 | 5.81 | 13.45 | 81.11 | 5.98 | 13.57 |

a) Br: Calcd. 29.41. Found 29.05 b) Br: Calcd. 27.97. Found 27.87

Table II. The Ultraviolet Spectral Data of 3-Arylindoles

| Compd No. | R | X | $\lambda_{max}^{EtOH}$ nm ($\varepsilon$) |
|---|---|---|---|
| **1b** | H | MeO | 228(24700), 266(17300), 290[hs](9000) |
| **1c** | Me | MeO | 237(25900), 266(16700), 300[hs](10000) |
| **1d** | H | Br | 225(30200), 284(17300) |
| **1e** | Me | Br | 228(30400), 298(16700) |
| **1f** | H | $NO_2$ | 220(30800), 281(8100), 286[sh](7700), 391(14800) |
| **1g** | Me | $NO_2$ | 226(28800), 288[sh](7000), 395(15300) |
| **1h** | H | $NH_2$ | 231(21200), 270(16400) |
| **6** | | | 230(30800), 295(19700), 358(9300) |

## Experimental[10]

**Methyl *p*-Methoxyphenylglycidate** (3a)——Following, Ban's procedure,[3] *p*-anisaldehyde (136 g, 1 mole) and methyl chloroacetate (108.5 g, 1 mole) were added to NaOMe in MeOH (prepared from 23 g of Na and

7) H.R. Snyder and C.W. Smith, *J. Am. Chem. Soc.*, **65**, 2452 (1943).
8) W. Wislicenus and F. Schultz, *Ann.*, **436**, 55 (1924).
9) E. Piers and R.K. Brown, *Can. J. Chem.*, **40**, 559 (1962).
10) Melting points are uncorrected. Infrared (IR) spectra were recorded on Hitachi G-3 model and Hitachi 215 spectrophotometers. Ultraviolet (UV) spectra were recorded on Hitachi EPS-3T spectrophotometer. Nuclear magnetic resonance (NMR) spectra were determined with JOEL JNM 4H-100 spectrometer with TMS as internal standard. Mass spectra were obtained on a Hitachi RMU-6E model.

400 ml of MeOH) at −10° during 30 min with stirring. The reaction mixture was stirred at −10° for 1 hr and at room temperature for 1 hr. The mixture was poured into $H_2O$ (1 liter) containing AcOH (7.4 ml), and the precipitates were collected. The precipitates gave crude **3a** (111 g, 63%), mp 58—62°, on one recrystallization from MeOH. Repeated recrystallizations from MeOH gave **3a**, mp 63—66°, as colorless plates. *Anal.* Calcd. for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.33; H, 5.78. IR $\nu_{max}^{KBr}$:cm$^{-1}$: 1728 (C=O). NMR ($CDCl_3$, ppm from TMS); 3.49 (d, 1H, $-\underset{O}{\underline{C}}H-CO$), 3.80 (s, 6H, MeO), 4.02 (d, 1H, $Ar-\underset{O}{\underline{C}}H-$).

***p*-Methoxyphenylacetaldehyde (5a)**——To a solution of **3a** (124.8 g, 0.6 mole) in benzene (500 ml) was added chilled MeOH–MeONa (prepared from 13.8 g of Na and 200 ml of MeOH). A small amount of $H_2O$ was added to the mixture to separate Na glycidate as white precipitates. The precipitates were collected and washed with benzene and MeOH. To a suspension of Na glycidate in benzene (600 ml) was added dropwise AcOH (45 g) in benzene (100 ml) at 55—60° during 1 hr. The evolution of $CO_2$ was detected with $Ba(OH)_2$. The mixture was refluxed for 2 hr to complete the decarboxylation. The benzene solution was washed with $H_2O$ and dried. The benzene was evaporated and the residue was distilled *in vacuo* to give **5a** (40.3 g, 40%), $bp_{4-6}$ 104—105°. IR $\nu_{max}^{film}$ cm$^{-1}$: 2710, 1730 (CHO), 1250, 1030 (C–O–C). NMR ($CDCl_3$): 3.60 (d, 2H, $CH_2$-CHO), 3.79 (s, 3H, OMe), 9.70 (t, 1H, CHO) Semicarbozone, mp 175—176° (reported mp 170—172° [5]).

**3-(*p*-Methoxyphenyl)indole (1b)**——A mixture of **5a** (40 g, 0.26 mole) and phenylhydrazine (28.8 g, 0.26 mole) in benzene (100 ml) was refluxed in an apparatus, equipped with a water separator for 3.5 hr, during which period about 3.5 ml of $H_2O$ was separated. The mixture was evaporated and the residue was dissolved in AcOH (100 ml). Boron trifluoride etherate (37.9 g) was added to the mixture, which was then refluxed for 2.5 hr (bath temperature 100—110°). The most of AcOH was evaporated and the residue was poured into $H_2O$ (1 liter), and the oil separated was extracted with benzene. The benzene extracts were neutrarized with aq. $NaHCO_3$, and washed with $H_2O$ and dried. The solvent was evaporated *in vacuo* to leave a residue (62.4 g) which was chromatographed over silica gel (200 g) column. The fractions eluted with benzene–hexane gave crude **1b** (30 g, 50%). Repeated recrystallizations from EtOH gave **1b**, mp 132—134°, as colorless crystals (reported mp,[11] 133—134°). NMR ($CDCl_3$): 3.82 (s, 3H, OMe), 8.06 (br. s, 1H, NH). IR $\nu_{max}^{KBr}$ cm$^{-1}$: 3400 (NH), 1250, 1030 (C–O–C). Mass Spectrum *m/e* (retive abundance): 223 ($M^+$, 100), 208(63), 180(9), 152(9), 111(8).

Fractions eluted with benzene gave a small amount of crystals which was recrystallized from benzene to give colorless plates, mp 139—141°. The structure has not been determined yet.

**Methyl *p*-Bromophenylglycidate (3b)**——To a chilled solution of *p*-bromobenzaldehyde (24.4 g, 0.133 mole) and methyl chloroacetate (21.5 g, 0.198 mole) in MeOH (100 ml) was added dropwise MeOH–MeONa (prepared from 4.55 g of Na and 100 ml of MeOH) under ice–salt cooling during 1 hr. After stirring the mixture at room temperature for 1 hr, further methyl chloroacetate (10.7 g × 2) and MeOH–MeONa (2.27 g of Na and 50 ml of MeOH, twice) were added to the mixture at room temperature. The mixture was stirred at room temperature for 1.5 hr. Since *p*-bromobenzaldehyde was still recognized by thin-layer chromatography (TLC) of the mixture, methyl chloroacetate (10.7 g) and MeOH–MeONa (same as above) were again added to the mixture. The whole mixture was stirred for another 1.5 hr at room temperature and poured into $H_2O$ (500 ml). The mixture was neutralized with AcOH to pH 6, and the oil separated was extracted with benzene. The benzene extracts were washed with $H_2O$, dried and evaporated. The residue (41 g) was chromatographed over silica gel (300 g) column. The fractions eluted with benzene–$CH_2Cl_2$ (3 : 1) gave crude **3b** (26 g, 82%), mp 55—57°. IR $\nu_{max}^{KBr}$ :1750 cm$^{-1}$ (C=O). NMR ($CDCl_3$): 3.42 (d, 1H, $-\underset{O}{\underline{C}}H-CO$), 3.75 (s, 3H, OMe), 4.02 (d, 1H, $Ar-\underset{O}{\underline{C}}H-$).

***p*-Bromophenylacetadehyde (5b)**——To a chilled solution of the above glycidate (26 g) in benzene was added a chilled MeOH–MeONa (Na(2.5 g) and MeOH(50 ml)) during 10 min. The mixture was stirred for 1 hr at room temperature, and $H_2O$ (4 ml) was added to the mixture to give the Na salt as white precipitates. The precipitates (22.6 g) were collected and washed with benzene and MeOH. The Na salt was made free[12] to give the glycidic acid (17.4 g), mp 125—130°. A suspension of the glycidic acid (10.4 g) in xylene (150 ml) was refluxed for 6 hr under $N_2$ atmosphere until the evolution of $CO_2$ ceased. The solvent was evaporated *in vacuo* and the residue was extracted with benzene and $H_2O$. The benzene solution was washed with aq. $NaHCO_3$, $H_2O$ and dried. The benzene solution was evaporated to leave an oil (4.84 g, 52%). IR $\nu_{max}^{film}$: 2720, 1730 cm$^{-1}$ (CHO). Mass Spectrum *m/e*: (relative aboundance) 200 (M+2, 35), 198($M^+$, 33), 171(100), 169(100), 106(30), 105(14), 91(61), 90(36), 89(23), 77(10). 2,4-Dinitrophenylhydrazone, mp 144—148° (from EtOH) (reported mp 153—154°[6]).

**3-*p*-Bromophenylindole (1d)**——A solution of *p*-bromophenylacetaldehyde (14 g) and phenylhydrazine (10.8 g) in benzene was refluxed for 3.5 hr. The benzene was evaporated to leave an oil which was dissolved

11) J. Szmuszkovicz, E.M. Glenn, J.B. Hester, and G.A. Youngdale, *J. Med. Chem.*, **9**, 527 (1966); J.M. Bruce, *J. Chem. Soc.*, **1959**, 2366.

12) H. Dahn, L. Loewe, and H. Hauth, *Helv. Chim. Acta*, **40**, 1521 (1957).

in AcOH (100 ml). Boron trifluoride etherate (9.9 g) was added to the solution. The mixture was refluxed for 2.5 hr and the solvent was concentrated to a small volume and the residue was poured into $H_2O$ (500 ml). The mixture was made alkaline with 20% NaOH, and the oil separated was extracted with benzene. The benzene extracts were washed with $H_2O$ and dried. The benzene was evaporated to leave an oil (14 g) which was chromatographed over silica gel (200 g) column. The fractions eluted with benzene gave crude **1d** (6.6 g, 40%). Repeated recrystallizations from benzene–hexane to give **1d**, mp 142—143°, as colorless crystals. NMR ($CDCl_3$): 8.15 (br. s, NH). Mass Spectrum *m/e* (relative abundance): 273($M^+$+2,100), 271($M^+$, 100), 191(28), 165(85), 96(37), 83(46).

**3-(*p*-Nitrophenyl)indole (1f)**——i) Preparation of 2-Carboxy-3-(*p*-nitrophenyl)indole (**9**): A mixture of 2-ethoxycarbonyl-3-(*p*-nitrophenyl)indole[8] (1.0 g) in 1% aq. KHO(100 ml) was refluxed for 4 hr. The solution was acidified with 10% HCl to precipitate the carboxylic acid (820 mg), mp 275—285°.

ii) Preparation of Copper Salt of 2-Carboxy-3-(*p*-nitrophenyl)indole[9]: A mixture of the ester (280 mg) in aq. $Na_2CO_3$ (53 mg) in $H_2O$ (40 ml) was refluxed for 30 min. After cooling, $CuSO_4$ $5H_2O$ (125 mg) in $H_2O$ (20 ml) was added to the solution to give green precipitates. The precipitates were collected and dried *in vacuo* to give crude copper salt (200 mg).

iii) The Decarboxylation: A mixture of the carboxylic acid (**9**) (3.1 g) and the copper salt (150 mg) in quinoline (120 ml) was heated at 220° (bath temperature) for 4 hr. The mixture was poured into 10% HCl and the separated oil was extracted with $CH_2Cl_2$. The extracts were washed with $H_2O$, dried and evaporated. The residue (4.2 g) was chromatographed over silica gel (50 g). Fractions eluted with benzene gave crude 3-(*p*-nitrophenyl)indole (**1f**) (2.5 g) 90%) as orange plates. Recrystallizations from benzene gave **1f**, mp 168—171°, as orange plates. NMR ($CDCl_3$): 8.30 (br. s, NH). Mass Spectrum *m/e* (relative abundance): 238($M^+$, 100), 208(16), 192(30). This indole did not develop purple color with the Ehrlich reagent.

**3-(*p*-Aminophenyl)indole (1h)**——To a boiling solution of **1f** (1.42 g) in conc. HCl (7 ml) and EtOH (50 ml) was added Fe powder (1.2 g) portionwise during 20 min. The mixture was further refluxed for 2 hr. The mixture was filtered to remove insoluble materials and evaporated *in vacuo* to leave a residue. The residue was made alkaline with 10% NaOH and extracted with $CH_2Cl_2$. The extracts were washed with $H_2O$, dried and evaporated to leave a solid (800 mg, 64%). The solid was purified through silica gel column and recrystallized from benzene–hexane and further from benzene gave **1h**, mp 159—161°, as pale brown crystals. IR $\nu_{max}^{KBr}$ $cm^{-1}$: 3430, 3350, 3150 (NH).

**Deamination of 1h *via* Its Diazonium Salt**——3-(*p*-Aminophenyl)indole (**1h**) (200 mg) was added to a boiling acidic solution (conc. HCl (3 ml) and $H_2O$ (30 ml)). After cooling, $NaNO_2$ (138 mg) in $H_2O$ (20 ml) was added to the mixture at 6—7°, which was stirred for 30 min at the same temperature. The separated diazonium salt was collected and dissolved in chilled 30% $H_3PO_3$ (30 ml). The mixture was stirred at room temperature for 55 hr and extracted with $CH_2Cl_2$. The extracts were washed with $H_2O$, dried and evaporated. The residue (37 mg) was chromatographed over silica gel. Fractions eluted with benzene–hexane (1: 1) gave crude 3-phenylindole (16 mg). Recrystallization from benzene–hexane gave **1a**, mp 78°, as colorless crystals which was identical with an authentic sample in mix mp and IR spectra.

**N-Methylation of 3-Arylindoles**——i) 1-Methyl-3-(*p*-methoxyphenyl)indole (1c): 3-(*p*-Methoxyphenyl)-indole (5.0 g) in ether (10 ml) was added with stirring to a mixture of $NaNH_2$ in liq. $NH_3$ (prepared from 0.53 g of Na and 150 ml of liq. $NH_3$ in the presence of $Fe(NO_3)_3$) under cooling with dry ice–acetone. Then $CH_3I$ (3.3 g) in ether (12 ml) was added to the mixture during 15 min. The mixture was then stirred at room temperature to evaporate $NH_3$. The residue was extracted with benzene (100 ml) and $H_2O$ (100 ml). The benzene layer was washed with $H_2O$, dried and evaporated to leave a crude N-methyl derivative (5.1 g, 96%), mp 101—104°, which showed one spot on TLC. Recrystallizations from benzene gave **1c**, mp 107—109°, as colorless crystals.

Other N-methyl derivatives were prepared in the similar manner. When the crude products showed the presence of the starting material, N- methylated indoles were easily separated from the starting material by silica gel column.

ii) 1-Methyl-3-(*p*-nitrophenyl)indole (**1g**): A mixture of 3-(*p*-nitrophenyl)indole (820 mg) and $K_2CO_3$ (3.5 g) in acetone (50 ml) was stirred for 1 hr at room temperature. To the reddish colored mixture was added dropwise $CH_3I$ (0.5 g) in acetone (10 ml), and the mixture was stirred for another 2 hr at room temperature, and then refluxed for further 3 hr. The mixture was filtered to remove inorganic materials and the filtrate was evaporated. The residue was extracted with $CH_2Cl_2$ and $H_2O$. The $CH_2Cl_2$ solution was washed with $H_2O$, dried and evaporated to give the yellow crystalline residue (750 mg, 85%), which was identical with the sample obtained from $NH_3$–$NaNH_2$ method.

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