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Arylindoles. II.[1] N-Arylindole-3-carboxaldehydes and Their Derivatives[2]

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1-Phenyl-, and 1-nitrophenylindoles were subjected to the Vilsmeier–Haack reaction to give the corresponding 1-arylindole-3-carboxaldehyde in good yield. These aldehydes were condensed with nitromethane and hydroxylamine. The oximes were dehydrated to afford the 1-arylindole-3-carbonitriles(**3b**—**3d**). The Knoevenagal condensation of **ld** with ethyl cyanoacetate gave **5d** as a 1 : 1 mixture of *cis* and *trans* isomers.

Keywords——N-Nitrophenylindole-3-carboxaldehydes; N-Nitrophenylindole-3-carbonitriles; N-Aryl-3-nitrovinylindoles; Knoevenagal condensation; Vilsmeier–Haack formylation

There are several patents on some N-arylindoles which have biological activity[4] or various uses as agents in color photography,[5] in agriculture,[6] and in other fields.[7] In our knowledge no systematic work has been carried out on the chemistry of N-aryl-indoles. From such a viewpoint we have initiated a program to study the synthesis and reactivity of these substituted indoles.

We had reported the synthesis of some N-arylindoles by Ullmann reaction.[1] Now we would like to report the formylation of some of these indoles and their conversion to some other derivatives.

It is well known that many indole derivatives give 3-carboxaldehyde products when subjected to Vilsmeier–Haack formylation.[8] N-Phenyl-, N-*o*-, *m*-, and *p*-nitrophenylindoles and the corresponding 2-phenyl derivatives could be derived from N-arylindoles by this method.[9] No difficulty was encountered during formylations of these indoles and the corresponding 3-carboxaldehydes (**1a**—**1g**) were obtained in excellent yields (see Chart 1). The occurrence of the substitution at C_3 of the indole nucleus was confirmed by the observation of their proton magnetic resonance (PMR) spectra. In the PMR spectrum of the aldehydes (**1a**—**1g**) one proton singlet due to an aldehydic proton appears at *ca.* δ 10. In the infrared (IR) spectrum a carbonyl absorption was observed between 1648 and 1670 cm^{-1}.

We carried out some condensation reactions with these N-aryl-indole-3-carboxaldehydes. Treatment of **1a**—**1g** with hydroxylamine afforded the corresponding oximes (**2b**—**2d**) in good yields. On heating with acetic anhydride, these oximes provided the nitriles (**3b**—**3d**) in excellent yields. The condensation of the aldehydes (**la**—**ld**) with nitromethane in the presence of ammonium acetate afforded the nitrovinyl derivatives (**4a**—**4d**) in good yields. In

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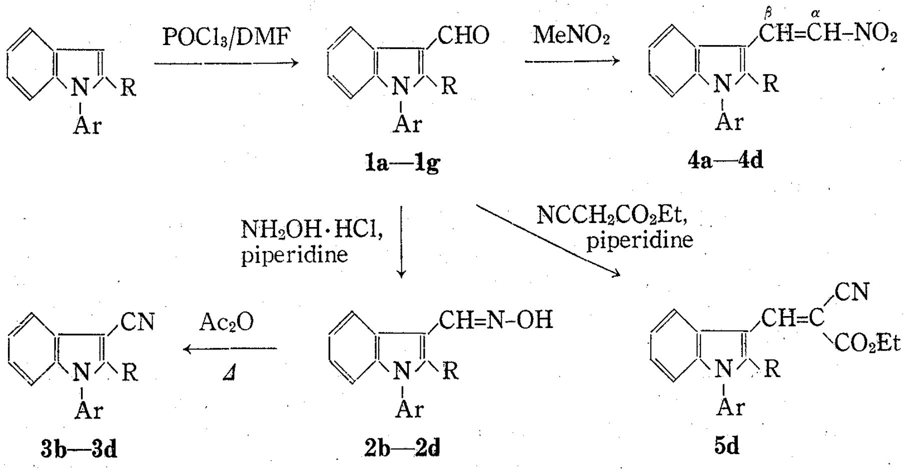
1) Part I: M.A. Khan and E.K. Rocha, *Chem. Pharm. Bull.* (Tokyo), **25**, 3110 (1977).
2) Taken in part from the Master's thesis of Emely Kazan Rocha, Instituto Militar de Engenharia, 1976.
3) Location: *Urca, Rio de Janeiro, RJ, Brasil.*
4) *a*) S. Archer and J.W. Schulenberg, U.S. Patent, 3189617 (1965) [*C.A.*, **63**, 11509 (1965)]; *b*) C.A. Rodriguez and P.R. Leeming, Brit. Patent, 1220628 (1971) [*C.A.*, **75**, 5690 (1971)]; *c*) H. Demarne, Ger. Offen., 2307707 (1973) [*C.A.*, **80**, 3379 (1974)]; *d*) *Idem, ibid.*, 2307708 (1973) [*C.A.*, **80**, 3381 (1974)].
5) D.D. Chapman, Ger. Offen., 1937251 (1970) [*C.A.*, **73**, 89168 (1970)].
6) *a*) J.K. Chakrabarti and A. Todd, Ger. Offen., 2117100 (1971) [*C.A.*, **76**, 46220 (1972)]; *b*) *Idem*, U.S. Patent, 3681332 (1971) [*C.A.*, **77**, 140158 (1972)].
7) D.L. Horrocks and H.O. Wirth, U.S. Patent, 3478208 (1969) [*C.A.*, **72**, 43438 (1970)].
8) W.J. Houlihan, "Indoles," Part I, the Chemistry of Heterocyclic Compounds, Ed. by A. Weissberger and E.C. Taylor, Wiley-Interscience, New York, 1972, p. 116, and references therein.
9) "Org. Synthesis," Coll. Vol., **4**, 539 (1967).

order to examine the possibility of participation of N-arylindole-3-carboxaldehydes in the Knoevenagal reaction,[10] **1d** was treated with ethyl cyanoacetate in ethanol in the presence of piperidine to give the desired product (**5d**) in 84% yield.

A detailed analysis of the PMR spectra was not possible at this stage due to the low solubilities of most of these derivatives. However, it seems that the nitrovinyl derivatives (**4**) exist in the *trans* form, because, in the PMR spectrum of the compounds which are relatively dissolved well, the vinyl proton appeared as an AB quartet having a large coupling constant (14 Hz). While in the case of cyanoacetate **5d**, it seems to be a mixture of equal amounts of *cis* and *trans* isomers since two distinct signals integrating for equal number of protons due to two ester groups (δ 0.71, 3.94 and δ 1.42, 4.36) were observed in its PMR spectrum.



a : R=H, Ar=Ph; **b** : R=H, Ar=*o*-$NO_2C_6H_4$; **c** : R=H, Ar=*m*-$NO_2C_6H_4$; **d** : R=H, Ar=*p*-$NO_2C_6H_4$; **e** : R=Ph, Ar=*o*-$NO_2C_6H_4$; **f** : R=Ph, Ar=*m*-$NO_2C_6H_4$; **g** : R=Ph, Ar=*p*-$NO_2C_6H_4$

Chart 1

Experimental

The PMR spectra were obtained on a Hitachi Perkin–Elmer model R-20B spectrometer operating at 60 Mc/s (tetramethylsilane as an internal standard). The IR absorption spectra were taken by the Perkin-Elmer model 727 spectrophotometer and were measured in potassium bromide disks. Melting points (mp) were determined with a Fisher–Johns apparatus and are uncorrected.

Formylations——General Procedure[9]: N,N-Dimethylformamide (0.4 mol) was added dropwise to cooled (0—5°) phosphoryl chloride (0.1 mol) and kept with stirring for 30 minutes. To the mixture, N-arylindole (0.1 mol dissolved in N,N-dimethylformamide) was added during 45—75 minutes. After addition, the mixture was allowed to reach the room temperature and kept at this temperature for further hour. Crushed ice was then added to the reaction mixture and made alkaline with sodium hydroxide solution (25%). After keeping overnight in the refrigerator, the precipitate was filtered, washed well with water, dried and recrystallized. The following compounds **1a**—**1g** were obtained by this metod.

1-Phenylindole-3-carboxaldehyde (**1a**): Formylation of 1 g of 1-phenylindole gave 1.12 g (98%) of 1a, mp 77—78° (aqueous ethanol), identical (mp, mixed mp, IR and PMR spectra) with the product of Ullmann arylation.[1]

1-*o*-Nitrophenylindole-3-carboxaldehyde (**1b**): Formylation of 4 g of 1-*o*-nitrophenylindole gave 4.12 g (92%) of **1b**, mp 128° (aqueous ethanol), identical (mp, mixed mp, IR, and PMR spectra) with the Ullmann arylation product.[1]

1-*m*-Nitrophenylindole-3-carboxaldehyde (**1c**): From the formylation of 4 g of 1-*m*-nitrophenylindole, 4.02 g (90%) of **1c**, mp 188—189° (aqueous ethanol) was obtained, identical (mp, mixed mp, IR, and PMR spectra) with the Ullmann arylation product.[1]

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10) G. Jones, *Org. Reactions*, **15**, 238 (1967).

1-*p*-Nitrophenylindole-3-carboxaldehyde (**1d**): From the formylation of 2 g of 1-*p*-nitrophenylindole there was obtained 2.18 g (98%) of **1d**, mp 268—269° (dec.) (aqueous ethanol), identical (mp, mixed mp, and IR spectrum) with the Ullmann arylation product.[1]

1-*o*-Nitrophenyl-2-phenylindole-3-carboxaldehyde (**1e**): The formylation of 1-*o*-nitrophenyl-2-phenylindole[1] (0.2 g) gave 0.15 g (68%) of **1e**, mp 242—243° (dec.) (aqueous ethanol). IR ν_{max} cm^{-1}: 3085, 1655 (C=O), 1600, 1523 (NO_2), 1472, 1451, 1345 (NO_2), 775, 752, 742, 725, 700. PMR ($CDCl_3$) δ: 7.02—8.50 (13H, m, arom.), 9.88 (1H, s, C$\underline{H}$O). *Anal.* Calcd. for $C_{21}H_{14}N_2O_3$: C, 73.75; H, 4.12; N, 8.19. Found: C, 73.68; H, 4.12; N, 8.18.

1-*m*-Nitrophenyl-2-phenylindole-3-carboxaldehyde (**1f**): From the formylation of 0.2 g of 1-*m*-nitrophenyl-2-phenylindole,[1] 0.21 g (95%) of **1f**, mp 247—248° (aqueous ethanol) was obtained. IR ν_{max} cm^{-1}: 3080, 1648 (C=O), 1590, 1521 (NO_2), 1498, 1345 (NO_2), 750, 735, 718. PMR ($CDCl_3$) δ: 7.14—8.58 (13H, m, arom.), 9.92 (1H, s, C$\underline{H}$O). *Anal.* Calcd. for $C_{21}H_{14}N_2O_3$: C, 73.75; H, 4.12; N, 8.19. Found: C, 73.60; H, 4.10; N, 8.16.

1-*p*-Nitrophenyl-2-phenylindole-3-carboxaldehyde (**1g**): The formylation of 0.2 g of 1-*p*-nitrophenyl-2-phenylindole[1] gave 0.21 g (98%) of **1g**, mp 189—190° (aqueous ethanol). IR ν_{max} cm^{-1}: 3080—3060, 1655 (C=O), 1605, 1530 (NO_2), 1475, 1450, 1345 (NO_2), 800, 745, 730, 705 PMR ($CDCl_3$) δ: 7.12—8.59 (13H, m, arom), 9.90 (1H, s, C$\underline{H}$O). *Anal.* Calcd. for $C_{21}H_{14}N_2O_3$: C, 73.75; H, 4.12; N, 8.19. Found: C, 73.80; H, 4.00; N, 8.02.

Oximes——General Procedure: A mixture of aldehyde **1b**—**d** (5.3 mmol), 2.2 g (32 mmol) of hydroxylamine hydrochloride and 7.5 ml of dry pyridine in 15 ml of absolute ethanol, was heated under reflux for 2 hr. The solvent was distilled off and the residue diluted with 30 ml of water, filtered, washed with water and recrystallized. The following oximes were obtained by this method.

1-*o*-Nitrophenylindole-3-carboxaldehyde Oxime (**2b**): From 0.72 g of **1b** was obtained 0.52 g (69%) of **2b**, mp 154—155° (aqueous ethanol). IR ν_{max} cm^{-1}: 3200—3150 (br., OH), 3100—3030, 1630 (br.), 1600, 1525 (NO_2), 1495, 1460, 1350 (NO_2), 925, 870, 850, 780, 745, 705. PMR ($CDCl_3$–DMSO-d_6) δ: 7.04—8.40 (10H, m, arom. and C$\underline{H}$=N-), 10.63 (1H, s, O$\underline{H}$). *Anal.* Calcd. for $C_{15}H_{11}N_3O_3$: C, 64.11; H, 3.94; N, 14.95. Found: C, 63.90; H, 3.96; N, 14.90.

1-*m*-Nitrophenylindole-3-carboxaldehyde Oxime (**2c**): From 1.43 g of **1c** was obtained 1.2 g (79%) of the oxime **2c**, mp 186—187° (ethanol). IR ν_{max} cm^{-1}: 3300—3160 (br., OH), 3120—3060, 1630, 1590, 1550, 1525 (NO_2), 1480, 1455, 1445, 1350 (NO_2), 950, 868, 802, 760, 750, 680. PMR ($CDCl_3$–DMSO-d_6) δ: 7.10—8.50 (10H, m, arom. and C$\underline{H}$=N-), 10.35 (1H, s, O$\underline{H}$). *Anal.* Calcd. for $C_{15}H_{11}N_3O_3$: C, 64.11; H, 3.94; N, 14.95. Found: C, 63.99; H, 3.80; N, 14.80.

1-*p*-Nitrophenylindole-3-carboxaldehyde Oxime (**2d**): From 0.72 g of **1d** was obtained 0.72 g (95%) of the oxime **2d**, mp 214—216° (dec.) (ethanol). IR ν_{max} cm^{-1}: 3300—3150 (br. OH), 3140—3050, 1630, 1595, 1550, 1525 (NO_2), 1500, 1460, 1350 (NO_2), 950, 850, 745, 690. PMR ($CDCl_3$–DMSO-d_6) δ: 7.10—8.50 (10H, m, arom. and C$\underline{H}$=N-), 10.68 (1H, s, O$\underline{H}$). *Anal.* Calcd. for $C_{15}H_{11}N_3O_3$: C, 64.11; H, 3.94; N, 14.95. Found: C, 63.99; H, 4.07, N, 14.68.

Nitriles——General Procedure: A mixture of N-arylindole-3-carboxaldehyde oxime (1 mmol) and 2.5 ml of acetic anhydride was heated under reflux for 4 hr. After cooling, the reaction mixture was added to 10 ml of water, filtered and recrystallized. The following nitriles were obtained in this way.

1-*o*-Nitrophenylindole-3-carbonitrile (**3b**): From 0.25 g of **2b** was obtained 0.21 g (88%) of the nitrile **3b**, mp 144—145° (aqueous ethanol). IR ν_{max} cm^{-1}: 3120—3050, 2220 (C≡N), 1605, 1530 (NO_2), 1494, 1455, 1342 (NO_2), 850, 780, 740, 698. PMR ($CDCl_3$) δ: 6.93—8.25 (m, arom.). *Anal.* Calcd. for $C_{15}H_9N_3O_2$: C, 68.50; H, 3.45; N, 15.98. Found: C, 68.42; H, 3.32; N, 15.96.

1-*m*-Nitrophenylindole-3-carbonitrile (**3c**): From 0.5 g of **2c** was obtained 0.45 g (96%) of **3c**, mp 205—207° (aqueous ethanol). IR ν_{max} cm^{-1}: 3120—3060, 2222 (C≡N), 1610, 1540, 1528 (NO_2), 1485, 1460, 1350 (NO_2), 805, 735, 690, 680. PMR ($CDCl_3$) δ: 7.20—8.40 (m, arom.). *Anal.* Calcd. for $C_{15}H_9N_3O_2$: C, 68.50; H, 3.45; N, 15.98. Found: C, 68.34; H, 3.45; N, 15.70.

1-*p*-Nitrophenylindole-3-carbonitrile (**3d**): This was obtained from 0.25 g of **2d** in a yield of 0.2 g (87%), mp 254—255° (dec.) (aqueous ethanol). IR ν_{max} cm^{-1}: 3120—3060, 2222 (C≡N), 1610, 1540, 1525 (NO_2), 1480, 1455, 1350 (NO_2), 810, 735, 690, 680. Insoluble in common solvents for PMR spectrum. *Anal.* Calcd. for $C_{15}H_9N_3O_2$: C, 68.50; H, 3.45; N, 15.98. Found: C, 68.51; H, 3.40; N, 15.89.

Condensation with Nitromethane——General Procedure[11]: A mixture of 0.05 mol of N-arylindole-3-carboxaldehyde, 0.075 mol of nitromethane, and ammonium acetate was heated with stirring on a water bath for 2—3 hr. The reaction mixture was allowed to cool to the room temperature and the precipitate was filtered, washed with hot water and recrystallized. The following nitrovinylindoles were thus prepared.

1-Phenyl-3-(2-nitrovinyl)indole (**4a**): Heating of a mixture of 1 g of **1a**, 4 ml of nitromethane, and 0.4 g of ammonium acetate for 3 hr gave 1.06 g (89%) of **4a**, mp 156.5—157.5° (aqueous acetone). IR ν_{max} cm^{-1}: 3120—3050, 1620 (C=C), 1590, 1540(NO_2), 1500, 1455, 1320 (NO_2), 805, 740, 695. PMR ($CDCl_3$) δ: 7.18—8.40

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11) B.A. Whittle and E.H.P. Young, *J. Med. Chem.*, **6**, 378 (1963).

(10H, m, arom.), 7.72 (1H, d, $J=14$ Hz, C$^{\alpha}$H), 8.25 (1H, d, $J=14$ Hz, C$^{\beta}$H). *Anal.* Calcd. for $C_{16}H_{12}N_2O_2$: C, 72.79; H, 4.58; N, 10.61. Found: C, 72.69; H, 4.50; N, 10.40.

1-*o*-Nitrophenyl-3-(2-nitrovinyl)indole (**4b**): Heating of a mixture of 0.25 g of **1b**, 0.6 ml of nitromethane, and 0.1 g of ammonium acetate for 2 hr gave 0.27 g (91%) of **4b**, mp 248—249° (dec.) (aqueous acetone). IR ν_{max} cm^{-1}: 3120—3050, 1630 (C=C), 1608, 1532 (NO_2), 1500, 1490, 1480, 1460, 1450, 1345 (NO_2), 1310, 970 (*trans* olef. C=C), 850, 805, 782, 760, 742, 700. PMR ($CDCl_3$-DMSO-d_6) δ: 7.00—8.50 (9H, m, arom.), 7.92 (1H, d, $J=14$ Hz, C$^{\alpha}$H), 8.35 (1H, d, $J=14$ Hz, C$^{\beta}$H). *Anal.* Calcd. for $C_{16}H_{11}N_3O_4$: C, 62.19; H, 3.58; N, 13.60. Found: C, 61.95; H, 3.52; N, 13.46.

1-*m*-Nitrophenyl-3-(2-nitrovinyl)indole (**4c**): Heating of a mixture of 0.25 g **1c**, 0.6 ml of nitromethane, and 0.1 g of ammonium acetate for 2 hr gave 0.26 g (88%) of **4c**, mp 248—249° (dec.) (aqueous acetone). IR ν_{max} cm^{-1}: 3120—3060, 1629 (C=C), 1588, 1534 (NO_2), 1495, 1475, 1460, 1345 (NO_2), 1310, 960 (*trans* olef. C=C), 865, 805, 755, 735, 685. PMR ($CDCl_3$-DMSO-d_6) δ: 7.20—8.50 (m, arom. and vinyl H). *Anal.* Calcd. for $C_{16}H_{11}N_3O_4$: C, 62.19; H, 3.58; N, 13.60. Found: C, 62.10; H, 3.60; N, 13.50.

1-*p*-Nitrophenyl-3-(2-nitrovinyl)indole (**4d**): Heating of a mixture of 0.25 g of **1d**, 0.6 ml of nitromethane, and 0.1 g of ammonium acetate for 2 hr gave 0.25 g (86%) of **4d**, mp 292—293° (dec.) (aqueous acetone). IR ν_{max} cm^{-1}: 3105—3080, 1628 (C=C), 1592, 1532 (NO_2), 1500, 1340 (NO_2), 1310, 960 (*trans* olef. C=C), 870, 850, 800, 735. PMR ($CDCl_3$-DMSO-d_6) δ: 7.10—8.50 (m, arom. and vinyl H). *Anal.* Calcd. for $C_{16}H_{11}N_3O_4$: C, 62.19; H, 3.58; N, 13.60. Found: C, 62.15; H, 3.52; N, 13.56.

Condensation with Ethyl Cyanoacetate——Ethyl α-cyano-β-(1-*p*-nitrophenylindole-3-yl)acrylate (**5d**): A mixture of 0.6 g (2 mmol) of **1d**, 0.23 g (2 mmol) of ethyl cyanoacetate and two drops of piperidine in 10 ml of ethanol was heated under reflux on a water bath for 6 hr. A part of the solvent was evaporated and the residue filtered, washed with water and dried. On crystallization with ethanol 0.69 g (84%) of **5d** was obtained. mp 175—176°. IR ν_{max} cm^{-1}: 3120—3020, 2220 (C≡N), 1720 (C=O, ester), 1594, 1525 (NO_2), 1460, 1348 (NO_2), 745, 682. PMR ($CDCl_3$) δ: 0.71 (1.5H, t, $J=6$ Hz), 1.42 (1.5H, t, $J=6$ Hz), 3.94 (1H, q, $J=6$ Hz), 4.36 (1H, q, $J=6$ Hz), 7.19—8.68 (10H, m, arom. and vinyl H). *Anal.* Calcd. for $C_{20}H_{15}N_3O_4$: C, 66.54; H, 4.19; N, 11.64. Found: C, 66.31; H, 4.20; N, 11.61.

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