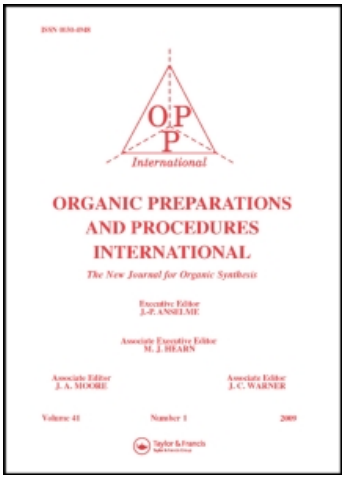

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AN IMPROVED FISCHER SYNTHESIS OF NITROINDOLES.

1,3-DIMETHYL-4-, 5- AND 6-NITROINDOLES

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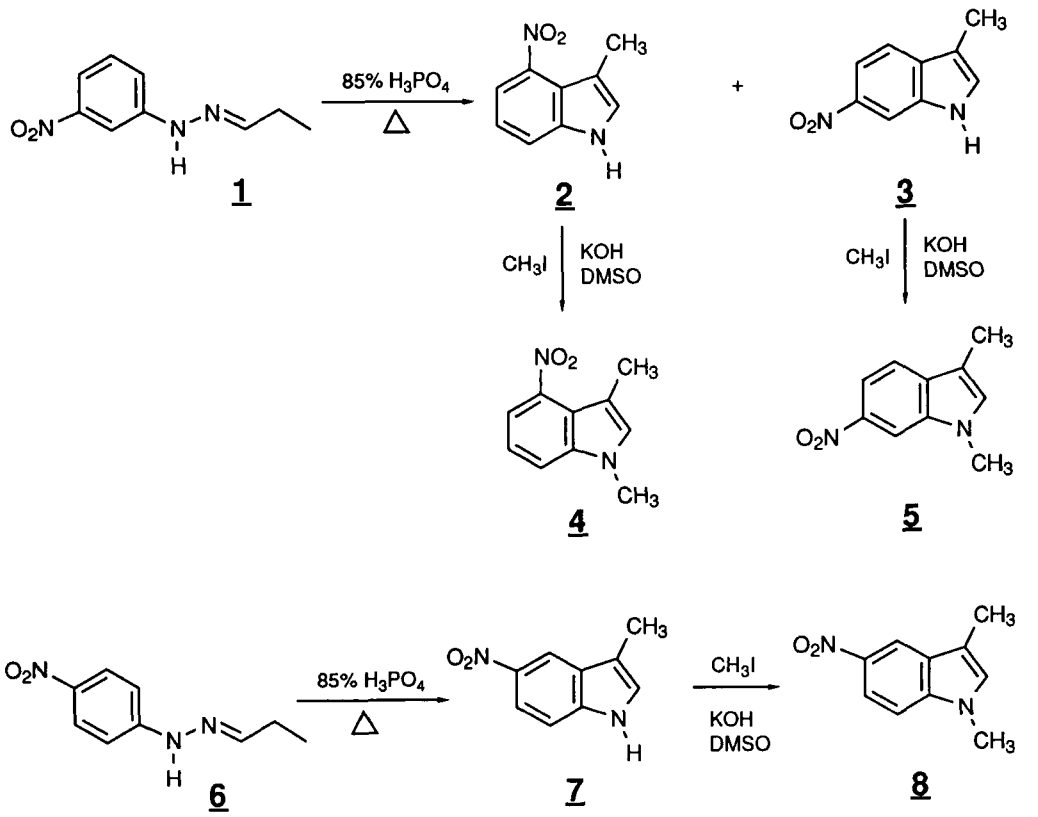
Nucleosides derived from 6-nitroindole are of biological interest.[1] Derivatives of 5-nitroindole are used in the synthesis of nitrazepan and hypnone.[2] Indoles bearing nitro substituents on the benzenoid ring can be reduced to the corresponding aminoindoles which are precursors to other biologically active compounds.[3-9] Unfortunately, there is no good general synthetic method for the preparation of such nitroindoles. Direct nitration of alkylindoles on the benzenoid ring is satisfactory only when both the 2 and 3 positions of the indole ring are substituted.[10] A single electron-withdrawing substituent at the indole 3-position also allows nitration of the benzenoid ring: thus, a mixture of 5- and 6-nitro derivatives was obtained upon nitration of indole-3-carboxaldehyde.[11] Addition of sodium bisulfite to unsubstituted indole gives 2,3-dihydro-2-indolesulfonic acid which after acylation of the nitrogen can be selectively nitrated at the 5-position giving, after hydrolysis, 5-nitroindole in 90% yield.[12] However, this method can not give other nitroindole isomers and also does not work with indoles substituted on the heterocyclic ring.

The Fischer synthesis[13-15] is the main route to indoles. Rydon and Siddappa reported in 1951 that the nitrophenylhydrazones (ortho, meta and para) derived from ethyl pyruvate did not undergo Fisher cyclization to indoles under any of several different sets of conditions.[16] However, Parmerter et al. later obtained ethyl 4-, 5-, 6- and 7-nitroindole-2-carboxylates by Fisher syntheses in polyphosporic acid with 19, 57, 8 and 66% yields, respectively.[17] In another report, ring closure of ethyl pyruvate o-nitrophenylhydrazone in polyphosphoric acid at 195° gave ethyl 7-nitro-2-indolecarboxylate in 13% yield.[18]

Several o-, m- and p-nitrophenylhydrazones derived from ketones were cyclized in hot concentrated hydrochloric acid to the corresponding 2,3-dialkylnitroindoles (5-nitro, 7-nitro and a mixture of 4- and 6-nitro) in 10-70% yields (the lowest yields were obtained for 4 and 6-nitroindoles).[19-20] 2,3-Dioxopiperidine 3-p-nitrophenylhydrazone was succesfully cyclized to 1,2,3,4-tetrahydro-6-nitro-1-oxo-β-carboline in polyphosphoric acid at 110°.[21] In general however, these methods cannot be used for the preparation of nitroindoles unsubstituted at position 2, i.e. by cyclization of nitrophenyl hydrazones of aldehydes. Two exceptions are: 3-ethyl-5-nitroindole was obtained from the 4-nitrophenylhydrazone of butyraldehyde in 25% yield by refluxing in concentrated hydrochloric acid,[23] cyclization of butyraldehyde-3-nitrophenylhydrazone in a benzene-concentrated hydrochloric acid two phase solvent system gave a mixture of 3-ethyl-4-nitroindole and 3-ethyl-6-nitroindole in 6 and 2% yields, respectively.[24] However, attempted ring closure of the 4-nitrophenylhydrazone of propionaldehyde by heating in concentrated hydrochloric acid gave 2,2'-propylidene-3,3'-dimethyl-5,5'-dinitroindole instead of the expected 3-methyl-5-nitroindole.[22] Other synthetic routes to such nitroindoles include catalytic dehydrogenation[4,25] of 2,3-dihydronitroindoles or their oxidation with DDQ[6] or oxygen in the presence a cobalt catalyst.[26] Cyclocondensation of dialkyl oxalates with formimidates derived from nitro-2-methylanilines,[27,28] and elimination of morpholine from 3-morpholino-2,3-dihydro-6-nitroindoles[29] have also been employed.

Our interest in 1,3-dimethylindoles bearing nitro substituents on the benzenoid rings encouraged us to search for a better synthetic method. 3-Nitroaniline was directly transformed in a one pot Fisher procedure[30] to a complex and difficult to separate reaction mixture containing 3-methyl-6-nitroindole 3 in a 6% yield (by NMR). Heating the 3-nitrophenylhydrazone of propionaldehyde[22] (1) with zinc chloride gave 3 in 5% yield with a trace of 3-methyl-4-nitroindole, but mainly unidentified resinous compounds. Heating the 4-nitrophenylhydrazone of propionaldehyde (6) with concentrated hydrochloric acid at 85-90° gave 3-methyl-5-nitroindole (7) in 8% yield. Finally, we found that utilization of phosphoric instead of hydrochloric acid in the Fischer procedure and simultaneous extraction of the product into toluene gave the desired indoles 2, 3 and 7 in good yields. Susequent methylation of these indoles by methyl iodide in DMSO in the presence of potassium hydroxide[31] gave crude 1,3-dimethylnitroindoles 4, 5 and 8. Purification of

the crude 7 by column chromatography afforded pure material in 70% yield.



A problem had to be solved with separation of nitroindoles 2 and 3. Thus, methylation of a mixture of indoles 2 and 3 gave a mixture of the corresponding 1,3-dimethylnitroindoles 4 and 5 but separation of this mixture appeared to be difficult; column chromatography and recrystallization from several solvents were attempted. We returned therefore to the mixture of 3-methylnitroindoles (2 and 3). Fractional recrystallization of 26 g of this mixture from ethanol/water gave a first fraction (3.4 g) containing 96% of 3, and a second fraction (4.5 g) containing 80% of 3. Recrystallization of the combined first and second fractions from ethanol gave analytically pure 3 (3.8 g). Evaporation of the mother liquors and recrystallization of 4.60 g of the residue from toluene gave 96% pure 3-methyl-4-nitroindole (1.82 g). Repeated recrystallization from toluene gave analytically pure 2. Finally methylation of 2 and 3 with methyl iodide in DMSO in the presence of KOH followed by chromatography of the crude products gave analytically pure samples of the 1,3-dimethyl-4- and -6-nitroindoles (4 and 5).

Reported ^{1}H NMR data on 5-nitroindoles,[32] and 6-nitroindoles[1] substituted on the pyrrole rings confirmed our assignments of the ^{1}H NMR spectra. Comparison of the ^{13}C NMR spectra of our nitroindoles with previously reported data[33-35] on variously substituted 4-, 5- and 6 nitroindoles allowed for their full assignments.

EXPERIMENTAL SECTION

Melting points: Hot-stage microscope. ^{1}H NMR: Varian VXR-300 NMR spectrometer (300 MHz) with TMS as the internal reference. ^{13} NMR: Varian VXR-300 NMR spectrometer (75 MHz), referenced to TMS; $CDCl_3$ was used as the solvent for both ^{1}H and ^{13}C NMR except where stated. Microanalyses: Dr. R. W. King (University of Florida).

Propionaldehyde 3-Nitrophenylhydrazone (1). - Treatment of 3-nitroaniline (100 g, 0.72 mol) in hydrochloric acid solution with sodium nitrite (60 g, 0.87 mol) followed by reduction of the obtained diazonium salt with tin (II) chloride according to the literature procedure[36] afforded crude 3-nitrophenylhydrazine hydrochloride. Sodium hydroxide (10%) was added slowly to a stirred suspension of this salt in ethanol (1000 ml) until the pH of the mixture reached 6. Acetic acid (500 ml) followed by propionaldehyde (36 ml, 0.50 mol) was added and the mixture was stirred at room temperature. After about 15 min, new crystals started to precipitate. Stirring was continued for 1 hr at room temperature followed by 30 min at 0°. The obtained precipitate was collected, washed with water and dried in the air to give propionaldehyde 3-nitrophenylhydrazone (94.13 g, 34% from 3-nitroaniline), mp. 85°, lit.[22] mp. 83°.

3-Methyl-4-nitroindole (2) and 3-methyl-6-nitroindole (3). - To a solution of propionaldehyde 3-nitrophenylhydrazone (35.3 g, 182 mmol) in toluene (1000 ml) was added 85% H_3PO_4 (200 ml) and the mixture was stirred at 100°C for 3 hrs. The toluene layer was decanted, fresh toluene (1000 ml) was added and the stirring at 100° continued for a further 6 hrs. Again the toluene layer was separated, the toluene solutions were combined and the solvent evaporated to give orange crystalline material (28.9 g). The ^{1}H NMR spectrum showed it to be a mixture of 3-methyl-4-nitroindole and 3-methyl-6-nitroindole in a ratio of 15:17 (yields: 42% and 48%, respectively). A mixture of the nitroindoles (26.00 g) was dissolved in 70% ethanol (400 ml) at 60° and stored at -5°C for 48 hrs. The resulting precipitate was collected, washed with a small amount of methanol and dried in air to

give a mixture of the 4- and 6-nitroindoles (3.41 g) in a ratio of 4:96. Dilution of the filtrate with water (100 ml) gave a second crop of the mixture (4.47 g) in a ratio of 20:80. Both crops were combined and recrystallized from 95% ethanol to give analytically pure 3-methyl-6-nitroindole 3 (3.8 g) as orange needles, mp. 148°. ^{1}H NMR: δ 2.36 (d, 3H, J = 1.1, Me), 7.28 (q, 1H, J = 1.1, H-2), 7.60 (d, 1H, J = 8.8, H-4), 8.02 (dd, 1H, J = 2.0 and 8.8, H-5), 8.33 (d, 1H, J = 2.0, H-7), 8.43 (bs, 1H, N-H). ^{13}C NMR: δ 9.5 (Me), 107.9 (C-7), 112.9 (C-3), 114.7 (C-5), 118.7 (C-4), 127.7 (C-2), 132.9 (C-3a), 134.6 (C-7a), 143.2 (C-6).

Anal. Calcd. for $C_9H_8N_2O_2$: C, 61.36; H, 4.58; N, 15.90. Found: C, 61.49; H, 4.58; N, 15.99

Concentration of the mother liquors gave a mixture of nitroindoles 2 and 3 (13.2 g) containing 80% of 2. A sample of this mixture (4.60 g) was recrystallized from toluene to give nitroindole 2 (1.82 g) of purity 96% (by ^{1}H NMR). Two more recrystallizations gave analytically pure isomer 2 as orange red needles, mp. 150°. ^{1}H NMR (DMSO): δ 2.37 (s, 3H, Me), 7.14 (t, 1H, J = 8.1, H-6), 7.23 (bs, 1H, H-2), 7.68 (d, 1H, J = 8.1, H-5), 7.72 (d, 1H, J = 7.8, H-7). ^{13}C NMR (DMSO): δ 13.0 (Me), 109.7 (C-3), 116.3 (C-5), 117.6 (C-7), 119.5 (C-6), 119.6 (C-3a), 128.1 (C-2), 139.5 (C-7a), 142.5 (C-4).

Anal. Calcd. for $C_9H_8N_2O_2$: C, 61.36; H, 4.58; N, 15.90. Found: C, 61.46; H, 4.48; N, 15.80

1,3-Dimethyl-6-nitroindole(5). - To a solution of 3-methyl-6-nitroindole (5.95 g, 34 mmol) in DMSO (50 ml) was added KOH (8.42 g, 150 mmol) and the obtained mixture was stirred at 25° for 2 hrs. Iodomethane (4.74 ml, 120 mmol) was then added and stirring was continued at room temperature for an additional 20 hrs. The mixture was poured into ice-water (200 g), neutralized with acetic acid and extracted with toluene (2 x 200 ml). The toluene solution was washed with water (2 x 200 ml), dried ($MgSO_4$) and the solvent evaporated under reduced pressure. The residue was subjected to column chromatography (silica gel-hexane/toluene/ethyl acetate - 10:10:1). The first fraction obtained was recrystallized from heptane/toluene (2:1) to give 1,3-dimethyl-6-nitroindole (3.91 g, 60%) as yellow needles, mp. 108°. ^{1}H NMR: δ 2.32 (d, 3H, J = 0.8, Me), 3.81 (s, 3H, N-Me), 7.10 (q, 1H, J = 0.8, H-2), 7.54 (d, 1H, J = 8.8, H-4), 7.96 (dd, 1H, J = 8.8 and 2.1, H-5), 8.22 (d, 1H, J = 2.1, H-7). ^{13}C NMR : δ 9.3 (Me), 32.9 (N-Me), 106.1 (C-7), 111.4 (C-3), 114.0 (C-5), 118.8 (C-4), 132.6 (C-2), 133.1 (C-3a), 135.1 (C-7a), 142.8 (C-6).

Anal. Calcd. for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.09; H, 5.22; N, 14.55

1,3-Dimethyl-4-nitroindole (4). - Using reaction conditions similar to the above, 2 (0.26 g, 1.5 mmol) was methylated with iodomethane (0.28 ml, 4.5 mmol) and KOH (0.25 g, 4.5 mmol) in DMSO (10 ml) to give (after recrystallization from heptane/toluene) pure 4 (0.12 g) as orange needles, mp. 105°. ^{1}H NMR: δ 2.37 (d, 3H, J = 0.9, Me), 3.78 (s, 3H, N-Me), 7.02 (m, 1H, H-2), 7.20 (t, 1H, J = 8.0, H-6), 7.51 (dd, 1H, J = 8.0 and 0.9, H-5), 7.78 (dd, 1H, J = 8.0 and 0.9, H-7). ^{13}C NMR: δ 12.9 (Me), 32.9 (N-Me), 109.9 (C-3), 114.9 (C-5), 116.6 (C-7), 120.0 (C-6), 120.1 (C-3a), 131.9 (C-2), 139.6 (C-7a), 143.0 (C-4).

Anal. Calcd. for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 62.78; H, 5.24; N, 14.64

3-Methyl-5-nitroindole (7). - A mixture of propionaldehyde p-nitrophenylhydrazone (25 g, 0.1 mol), 85% H_3PO_4 (150 ml) and toluene (500 ml) was vigorously stirred at 90-100° for 2 h and the reddish toluene phase was separated. Fresh toluene (500 ml) was added and the stirring at 90-100° was continued for 4 more hours. The toluene phase was separated again and the treatment repeated for the 3rd time (4 h). The toluene extracts were combined, dried (Na_2CO_3) and the solvent was removed under reduced pressure at 60° to give 3-methyl-5-nitroindole (19.30 g, 85%) as an orange solid. Recrystallization from hexane/EtOH gave yellow needles, mp.134-135°, lit.[37] mp. 127-130°. ^{1}H NMR: δ 2.36 (d, 3H, J = 1.1, CH_3), 7.14 (m, 1H, H-2), 7.38 (d, 1H, J = 9.0, H-7), 8.08 (dd, 1H, J = 1.9 and 9.0, H-6), 8.53 (d, 1H, J = 1.9, H-4), 8.59 (bs, 1H, N-H). ^{13}C NMR: δ 9.5 (CH_3), 11.0 (C-7), 114.3 (C-3), 116.4 (C-4), 117.5 (C-6), 124.8 (C-2), 127.8 (C-3a), 139.4 (C-5), 141.2 (C-7a).

1,3-Dimethyl-5-nitroindole (8) - 3-Methyl-5-nitroindole (17.6 g, 0.10 mol) was methylated with CH_3I (28.4 g, 0.2 mol) in DMSO (50 ml) in the presence of KOH (5.6 g, 0.1 mol) at 25° for 16 h with continuous stirring. The reaction mixture was poured into water (600 ml) and extracted with $CHCl_3$. The chloroform extract was dried over anhydrous Na_2CO_3 and the solvent removed at 50° under reduced pressure. The crude product was subjected to column chromatography (silica gel-hexane/AcOEt, 4:1) to yield pure 1,3-dimethyl-5-nitroindole (8) (13.2 g, 69.5%). An analytical sample, yellow needles, mp. 146-147° was obtained by recrystallization from 80% EtOH, ^{1}H NMR: δ 2.32 (d, 3H, J = 1.0, CH_3), 3.77 (s, 3H, N-CH_3), 6.95 (s, 1H, H-2), 7.23 (d, 1H, J = 9.0, H-7), 8.06 (dd, 1H, J = 2.2 and 9.0, H-6), 8.47 (d, J = 2.2, H-4). ^{13}C-NMR: δ 9.3 (CH_3), 32.9 (N-CH_3), 108.8 (C-7), 113.3 (C-3), 116.4 (C-4), 117.1 (C-6), 127.9 (C-3a), 129.6 (C-2), 139.7 (C-5), 140.8 (C-7a).

Anal. Calcd. for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.27; H, 5.35; N, 14.50

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