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Nitration of 3-Acylindoles in the Presence of Metal MeCN Solvates and Synthesis of the Antibiotic Alkaloid Chuangxinmycin

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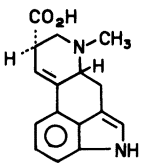
Nitration of 3-acylindoles in the presence of MeCN solvates of Cu^{2+}, Al^{3+}, and Fe^{2+} salts yielded 3-nitroindole, 4-nitro- and 6-nitro-3-acylindoles, of which 3-acetyl-4-nitroindole was subsequently transformed into dehydrochuangxinmycin (**7**), the dehydro derivative of the antibiotic alkaloid chuangxinmycin (**2**).

Keywords——nitration; 3-acylindole; metal MeCN solvate; 3-acetyl-4-nitroindole; synthesis; chuangxinmycin

Considerable interest has been focused on the direct C-4 substitution reaction of indoles in connection with the synthesis of C-4-substituted indole alkaloids, including the ergot family alkaloids (*e.g.* lysergic acid (**1**)) and chuangxinmycin (**2**). Although several direct C-4 substitution reactions of indole[1-4] have been developed, direct nitration or halogenation at C-4 of indoles has not been achieved to date. For example, nitration of 3-formyl- or 3-acetylindole in acidic media gave only a few percent of the 4-nitro derivative.[5,6] This paper deals with nitration of 3-acylindoles in the presence of metal acetonitrile (AN) solvates, $Cu(AN)_6(ClO_4)_2$, $Al(AN)_6(ClO_4)_3$, and $Fe(AN)_6(BF_4)_2$, to give the 4-nitro derivatives in significant yields. We also describe the subsequent transformation of the 3-acetyl-4-nitroindole (**3**) to dehydrochuangxinmycin (**7**), the dehydro derivative of the unique antibiotic alkaloid chuangxinmycin (**2**).



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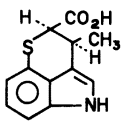

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Chart 1

Nitration of 3-Acylindoles in the Presence of Metal MeCN Solvates

The solvates in AN, $Cu(AN)_6(ClO_4)_2$, $Al(AN)_6(ClO_4)_3$, and $Fe(AN)_6(BF_4)_2$, were prepared from the corresponding metal salt hydrates, $Cu(ClO_4)_2 \cdot 6H_2O$, $Al(ClO_4)_3 \cdot 8H_2O$, and $Fe(BF_4)_2 \cdot 6H_2O$, in AN by the addition of 6 or 8 mol of Ac_2O to remove water.[7] Nitrations of 3-acetylindole and 3-formylindole (3-indolecarbaldehyde) were carried out with 99% HNO_3 in the presence of the metal solvates in AN. The results are shown in Table I.

On the other hand, nitration of 3-acylindoles in the presence of Lewis acids, namely, BF_3, BCl_3, $AlCl_3$, *etc.*, in AN, glyme or CH_2Cl_2 afforded only the 6-nitro derivatives as the main

TABLE I. Nitration of 3-Acylindoles in the Presence of Metal MeCN Solvates

Entry	Substituent	Catalyst	Position of nitration, yield (%)				Time (h)	Temp. (°C)
			3-	4-	6-	Recover		
1	3-Ac	A	38.4	20.5	25.4	—	1	15
2	3-Ac	B	16.1	12.3	24.3	7.2	2	13
3	3-Ac	C	28.2	20.8	31.9	—	3.5	15
4	3-Formyl	A	21.7	19.1	19.3	3.4	19	13
5	3-Formyl	B	9.6	15.5	22.1	18.4	4	5
6	3-Formyl	C	21.9	5.9	21.8	29.8	24	15

Metal complex: A, $Cu(AN)_6(ClO_4)_2$; B, $Al(AN)_8(ClO_4)_3$; C, $Fe(AN)_6(BF_4)_2$.

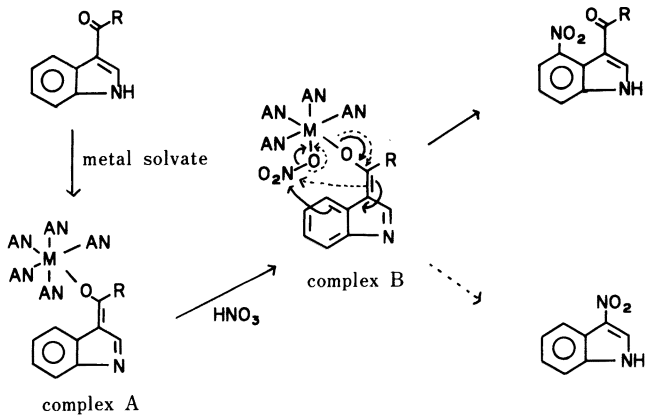

Chart 2

product. The formation of significant amounts of 4-nitro derivatives and 3-nitroindole in the nitration of 3-acylindoles in the presence of the metal AN solvates may depend on the involvement of complexes such as A and B, whose existence is supported by the color changes from light blue (complex A) to deep green (complex B) during the course of the reaction and by the solubility changes of 3-acylindoles (3-acylindoles are less soluble in AN without the metal solvates).

A New Synthesis of Methyl Dehydrochuangxinmycin

Chuangxinmycin (a new kind of mycin) (**2**) is an antibiotic alkaloid having a unique indole skeleton, isolated from the microorganism *Actinoplanes tsinanensis* n. sp. in China. This compound is known to be active *in vitro* against a number of gram-positive and gram-negative bacteria and to be active *in vivo* in mice against *Escherichia coli* and *Shigella dysenteria* infections. Preliminary clinical results have shown that chuangxinmycin is effective in the treatment of septicemia and urinary and biliary infections caused by *E. coli*.[8,9] The structure of **2** was confirmed by X-ray crystallography[10] and syntheses.[11,12] We synthesized dehydrochuangxinmycin (**7**) from 3-acetyl-4-nitroindole (**3**) prepared by means of the above reaction.

The 4-amino derivative **4** prepared by reduction of **3** by catalytic hydrogenation or with $TiCl_3$, was transformed to the 4-iodo compound **5**[13] through the diazonium salt. Novel displacement of iodine with thioacetate to give the methyl thioacetate **6** was performed by treatment of the iodide with methyl thioglycolate in pyridine–methanol in 95% yield.

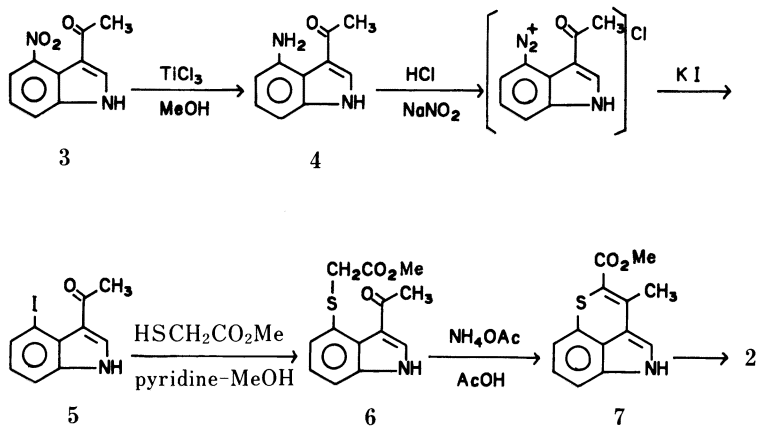

Chart 3

Treatment of the thioacetate **6** with ammonium acetate in AcOH afforded dehydrochuangxinmycin (**7**) in 93% yield. All physical data of the product **7** were identical with those given previously.[12] Thus, the formal synthesis of chuangxinmycin (**2**) by a new route was attained.

Experimental

All melting points are uncorrected. Infrared (IR) spectra were recorded with a Hitachi 260-10 spectrometer, proton nuclear magnetic resonance (^{1}H-NMR) spectra with a JEOL JNM-FX 100 or JEOL JNM-GX 270 spectrometer (with tetramethylsilane as an internal standard in $CDCl_3$, CD_3COCD_3 and dimethyl sulfoxide (DMSO)-d_6 solution) and mass spectra (MS) with a JEOL JMS-d 300 spectrometer. Wako Silica Gel C-200 (200 mesh) and Merck Kieselgel 60 F_{254} were used for column chromatography and thin layer chromatography (TLC), respectively.

Nitrations of 3-Acetylindole in the Presence of Metal AN Solvates——Method A: The solvate, $Cu(AN)_6(ClO_4)_2$, was prepared by the addition of 7.14 g (70 mmol) of Ac_2O to a solution of 3.70 g (10 mmol) of $Cu(ClO_4)_2 \cdot 6H_2O$ in AN (29 ml) at room temperature, and the mixture was stirred for 30 min. Then 1.59 g (10 mmol) of acetylindole was added and the mixture was stirred at room temperature for 30 min. At that time, the color of the solution changed from light blue to dark green.To the above mixture, 756 mg of HNO_3 (99%) in AN (1 ml) was added very slowly at 15 °C with stirring and the whole was stirred at the same temperature for 1 h. The precipitates (3-acetyl-6-nitroindole) were separated by filtration. The filtrate was poured into water and extracted with AcOEt. The organic layer was washed with sat. $NaHCO_3$ and brine. The AcOEt layer was dried and concentrated under vacuum. The residue was subjected to dry silica gel column chromatography. The first eluate with AcOEt–hexane (1 : 1) gave 623 mg (38.4%) of 3-nitroindole as light yellow needles (AcOEt–benzene), mp 213—214 °C. NMR (CD_3COCD_3) δ: 7.32—7.42 (2H, m, aromatic H), 7.59—7.65 (1H, m, aromatic H), 8.16—8.23 (1H, m, aromatic H), 8.49 (1H, s, C-2 H), and 11.54 (1H, br s, NH).[5a] The second eluate with the same solvent was combined with the previous precipitates and recrystallized from acetone to give 519 mg (25.4%) of 3-acetyl-6-nitroindole as brown crystals, mp 340—342 °C. NMR (CD_3COCD_3) δ: 2.53 (3H, s, $COCH_3$), 8.115 (1H, dd, J=9.28, 1.95 Hz, C-5 H), 8.43—8.58 (3H, m, aromatic H), 11.53 (1H, br s, NH).[5a] The third eluate afforded 420 mg (20.5%) of 3-acetyl-4-nitroindole as yellow needles (AcOEt), mp 229—230 °C. NMR (CD_3COCD_3) δ: 2.49 (3H, s, $COCH_3$), 7.39 (1H, t, J=7.81 Hz, C-6 H), 7.605 (1H, dd, J=7.8, 1 Hz, C-7 H), 7.85 (1H, dd, J=7.8, 1 Hz, C-5 H), 8.43 (1H, d, J=2.9 Hz, C-2 H), 11.53 (1H, br s, NH).[5a]

Method B: The solvate, $Al(AN)_6(ClO_4)_3$, was prepared with 4.69 g (10 mmol) of $Al(ClO_4)_3 \cdot 8H_2O$ and 9.18 g (90 mmol) of Ac_2O in 29 ml of AN. Nitration of 1.59 g (10 mmol) of 3-acetylindole was carried out with 756 mg of 99% HNO_3 in AN (1 ml) at 13 °C for 2 h. The reaction mixture was worked up as described in method A, and the residue obtained was purified according to method A to give 261 mg (16.1%) of 3-nitroindole, 114 mg (7.2%) of 3-acetylindole, 496 mg (24.3%) of 3-acetyl-6-nitroindole, and 252 mg (12.3%) of 3-acetyl-4-nitroindole.

Method C: The solvate, $Fe(AN)_6(BF_4)_2$, was prepared with 3.38 g (10 mmol) of $Fe(BF_4)_2 \cdot 6H_2O$ and 7.14 g (70 mmol) of Ac_2O in 29 ml of AN. Reaction of 1.59 g of 3-acetylindole in the presence of the solvate with 756 mg of 99% HNO_3 in AN (1 ml) was carried out at 15 °C for 3.5 h. The mixture was worked up as described in method A, and the residue obtained was purified according to method A to give 475 mg (28.2%) of 3-nitroindole, 652 mg (31.6%) of 3-acetyl-6-nitroindole, and 426 mg (20.8%) of 3-acetyl-4-nitroindole.

Nitration of 3-Indolecarbaldehyde in the Presence of Metal AN Solvates——Method A: 3-Indolecarbaldehyde

(1.45 g, 10 mmol) was added to a solution of the solvate, $Cu(AN)_6(ClO_4)_2$ [prepared from 3.70 g (10 mmol) of $Cu(ClO_4)_2 \cdot 6H_2O$ and 7.14 g (70 mmol) of Ac_2O], in 29 ml of AN as described for the reaction of 3-acetylindole above, and the mixture was stirred at room temperature for 30 min. Then 756 mg of 99% HNO_3 in AN (1 ml) was added very slowly at 13 °C and the whole was stirred at room temperature for 19 h. The reaction mixture was poured into water and extracted with AcOEt. The AcOEt layer was washed with sat. $NaHCO_3$ and brine. The organic layer was dried and concentrated under a vacuum. The residue was subjected to dry silica gel chromatography. The first eluate with AcOEt–hexane (1.5 : 2) gave 352 mg (21.7%) of 3-nitroindole as light yellow needles (AcOEt–benzene). The second eluate gave 49 mg (3.4%) of 3-indolecarbaldehyde. The third eluate with the same solvent afforded 368 mg (19.3%) of 6-nitro-3-indolecarbaldehyde as yellow crystals (acetone), mp 302—304 °C (dec.). NMR (DMSO-d_6) δ: 8.09 (1H, dd, J=8.79, 2 Hz, C-5 H), 8.25 (1H, d, J=8.79 Hz, C-4 H), 8.42 (1H, d, J=2 Hz, C-7 H), 8.65 (1H, s, C-2 H), 10.03 (1H, s, CHO), 12.65 (1H, br s, NH).[5b] The 4th eluate with the same solvent yielded 364 mg (19.1%) of 4-nitro-3-indolecarbaldehyde as orange needles (AcOEt–hexane), mp 190—192 °C. NMR (CD_3COCD_3) δ: 7.49 (1H, t, J=8.0 Hz, C-6 H), 7.96 (1H, dd, J=8.0, 0.7 Hz, C-7 H), 8.00 (1H, dd, J=8.0, 0.7 Hz, C-5 H), 8.43 (1H, s, C-2 H), 10.29 (1H, s, CHO), 11.84 (1H, s, NH).[5b]

Method B: The solvate, $Al(AN)_6(ClO_4)_3$, was prepared from 4.69 g (10 mmol) of $Al(ClO_4)_3 \cdot 8H_2O$ and 9.18 g (90 mmol) of Ac_2O in 29 ml of AN. Reaction of 1.45 g (10 mmol) of 3-indolecarbaldehyde in the presence of the solvate was carried out with 756 mg of 99% HNO_3 in AN (1 ml) at 5 °C for 4 h. The reaction mixture was worked up as described in method A and the residue obtained was purified according to method A to give 156 mg (9.6%) of 3-nitroindole, 267 mg (18.4%) of 3-indolecarbaldehyde, 420 mg (22.1%) of 6-nitro-3-indolecarbaldehyde, and 295 mg (15.5%) of 4-nitro-3-indolecarbaldehyde.

Method C: The solvate, $Fe(AN)_6(BF_4)_2$, was prepared with 3.38 g (10 mmol) of $Fe(BF_4)_2 \cdot 6H_2O$ and 7.14 g (70 mmol) of Ac_2O in AN (29 ml). Nitration of 1.45 g (10 mmol) of 3-indolecarbaldehyde with 765 mg of 99% HNO_3 in AN (1 ml) in the presence of the solvate was carried out at 15 °C for 24 h. The reaction mixture was worked up as described in method A, and purified according to method A to give 355 mg (21.9%) of 3-nitroindole, 430 mg (29.8%) of 3-indolecarbaldehyde, 415 mg (21.8%) of 6-nitro-3-indolecarbaldehyde, and 113 mg (5.9%) of 4-nitro-3-indolecarbaldehyde.

3-Acetyl-4-aminoindole (4)——A 31.8 ml portion of $TiCl_3$ solution (17—19%) was added at once to a suspension of 1.17 g of 3-acetyl-4-nitroindole (**3**) in MeOH (8 ml) and the mixture was stirred at room temperature for 1.5 h. The crystalline precipitates were separated by filtration, and washed with 23% HCl. The precipitates were dissolved in hot water, and then the solution was basified with sat. $NaHCO_3$. The basic solution was extracted with AcOEt. The organic layer was dried and concentrated. The residue was recrystallized from MeOH to give 980 mg (91.0%) of **4** as yellow crystals, mp 232—234 °C (dec.). IR (Nujol) cm^{-1}: 3425, 3280, 1590. NMR (CD_3COCD_3) δ: 2.48 (3H, s, $-COCH_3$), 5.6 (2H, br, NH_2), 6.32 (1H, dd, J=7.8, 1 Hz, C-5 H or C-7 H), 6.62 (1H, dd, J=8.3, 1 Hz, C-5 H or C-7 H), 6.92 (1H, dd, J=8.3, 7.8 Hz, C-6 H), 8.09 (1H, d, J=3.4 Hz, C-2 H), 10.8 (1H, br s, indole NH). MS m/z: Calcd for $C_{10}H_{10}N_2O$ (M^+): 174.0793. Found: 174.0811.

3-Acetyl-4-iodoindole (5)——A solution of 369 mg of $NaNO_2$ in water (9 ml) was added slowly to a solution of 422.8 mg of **4** in 2 N HCl with stirring at 0 °C. To the above diazonium salt solution, a solution of 25 g KI in water (18 ml) was added with stirring at 0 °C, and the whole was stirred at room temperature for 1 h and then at 85 °C for 10 min. After cooling, the mixture was extracted with AcOEt. The organic layer was washed with 5% $Na_2S_2O_3$ and brine. The AcOEt layer was dried and concentrated. The residue was subjected to dry silica gel chromatography, and the eluate with AcOEt–hexane (1 : 1.5) gave 505 mg (73%) of **5** as colorless needles (MeOH), mp 215—218 °C (dec.) (lit. mp 204—206 °C (dec.)).[13] IR (Nujol) cm^{-1}: 3140, 1640. NMR (CD_3COCD_3) δ: 2.50 (3H, s, $COCH_3$), 6.95 (1H, dd, J=8.3, 7.32 Hz, C-6 H), 7.56 (1H, dd, J=8.3, 1 Hz, C-5 H or C-7 H), 7.76 (1H, dd, J=7.32, 1 Hz, C-5 H or C-7 H), 8.23 (1H, d, J=2.93 Hz, C-2 H), 11.1 (1H, br s, NH), MS m/z: Calcd for $C_{10}H_8INO$ (M^+): 284.9646. Found: 284.9645. *Anal.* Calcd for $C_{10}H_8INO$: C, 42.13; H, 2.83; N, 4.91. Found: C, 42.20; H, 2.93; N, 4.62.

Methyl [(3-Acetyl-4-indolyl)thio]acetate (6)——A solution of 28.5 mg of **5**, 34 mg of methyl thioglycolate and 26.1 mg of pyridine in MeOH (1 ml) was heated at 90 °C under a nitrogen atmosphere for 48 h. Water was added to the mixture, and the whole was extracted with AcOEt. The organic layer was washed with dil. HCl, sat. $NaHCO_3$, and brine. The AcOEt layer was dried and concentrated. The residue was recrystallized from benzene to give 26 mg (95%) of **6** as colorless needles, mp 140—141.5 °C. NMR ($CDCl_3$) δ: 2.48 (3H, s, $COCH_3$), 3.72 (3H, s, CO_2CH_3), 3.78 (2H, s, $-SCH_2-$), 7.08—7.19 (3H, m, aromatic H), 7.69 (1H, d, C-2 H), 9.47 (1H, br s, NH). Ethyl [(3-acetyl-4-indolyl)thio]acetate was prepared by similar reaction of **5** and ethyl thioglycolate: mp 140—141 °C (MeOH). IR (Nujol) cm^{-1}: 3160, 1719, 1619. NMR (CD_3COCD_3) δ: 1.18 (3H, t, J=7.1 Hz, $COCH_2\underline{CH_3}$), 2.49 (3H, s, $COCH_3$), 3.74 (2H, s, $-SCH_2-$), 4.11 (2H, q, J=7.1 Hz, $CO\underline{CH_2}CH_3$), 7.14 (1H, dd, J=7, 2 Hz, C-5 H or C-7 H), 7.18 (1H, t, J=7 Hz, C-6 H), 7.32 (1H, dd, J=7, 2 Hz, C-5 H or C-7 H), 8.20 (1H, d, J=3.2 Hz, C-2 H), 11.05 (1H, br s, NH). MS m/z: Calcd for $C_{14}H_{15}NO_3S$ (M^+): 277.077. Found: 277.0763.

Dehydrochuangxinmycin Methyl Ester (7)——A mixture of 108 mg of **6**, 144 mg of ammonium acetate monohydrate, and 277 mg of AcOH in benzene (8 ml) was heated at 110 °C for 15 h under a nitrogen atmosphere. Water was added to the mixture, and the whole was extracted with AcOEt. The organic layer was washed with sat. $NaHCO_3$ and brine. The AcOEt layer was dried and concentrated. The residue was recrystallized from benzene to

give 93 mg (93%) of methyl dehydrochuangxinmycin (**7**) as yellow needles, mp 167—168 °C.[12a] NMR ($CDCl_3$) δ: 2.34 (3H, s, CH_3), 3.81 (3H, s, CO_2CH_3), 6.51—6.94 (4H, m, aromatic H), 7.91 (1H, br s, NH). *Anal.* Calcd for $C_{13}H_{11}NO_2S$: C, 63.67; H, 4.52; N, 5.71. Found: C, 63.63; H, 4.68; N, 5.44. Ethyl dehydrochuangxinmycin was prepared by similar reaction of ethyl [(3-acetyl-4-indolyl)thio]acetate: mp 183—185 °C (MeOH). IR (Nujol) cm^{-1}: 3250, 1640. NMR (CD_3COCD_3) δ: 1.31 (3H, t, $J=7$ Hz, $CO_2CH_2\underline{CH_3}$), 2.32 (3H, s, CH_3), 4.22 (2H, q, $J=7$ Hz, $CO_2\underline{CH_2}CH_3$), 6.46 (1H, dd, $J=7$, 1.1 Hz, C-8 H or C-10 H), 6.81—6.91 (2H, m, aromatic H), 7.25 (1H, d, $J=2.5$ Hz, C-2 H), 10.32 (1H, br s, NH). *Anal.* Calcd for $C_{14}H_{13}NO_2S$: C, 64.84; H, 5.05; N, 5.40. Found: C, 64.64; H, 5.16: N, 5.19.

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