Chemoselective Reductions of 2-Acyl-1*H*-indole-3-carboxaldehydes

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A novel procedure for the chemoselective reduction of 2-acyl-1*H*-indole-3-carboxaldehydes has been developed. Low temperature lithium triethylborohydride reduction affords the indol-2-yl carbinol whilst sodium cyanoborohydride reduction in acetic acid affords the 3-hydroxymethyl analogs. Both processes are high yield, and provide access to intermediates of potential utility for indole alkaloid synthesis.

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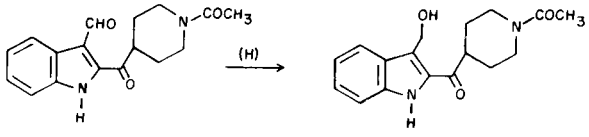
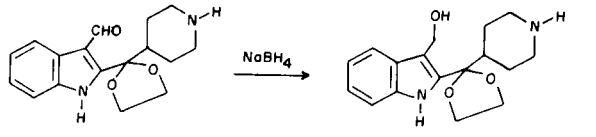
During the course of our studies directed towards the total synthesis of the unique indole alkaloid apparicine [2] we were confronted by the transformation shown in equation I.



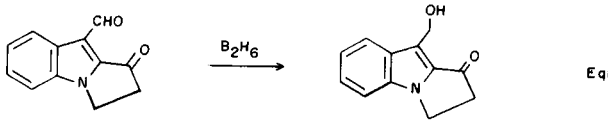
Eqn. I

This step was envisaged as being of prime importance in the synthesis mentioned above and of gramine type compounds in general. A survey of the literature [3] on the reduction of 2- or 3-acyl indoles to their respective alcohols suggested that this transformation may not be a facile process.

The reactivity of a carbonyl group in the indole 3-position is affected by its direct conjugation with the indole nitrogen, to the extent that its reactivity tends to become less than that of a carbonyl group on a benzene ring towards nucleophiles. In addition, the bonding in indole 3-carbonyl compounds apparently differs considerably from that in other aromatic aldehydes, since certain of the former undergo 1,4 addition [4].



Eqn. II



Eqn. III

Joule [5] had used sodium borohydride to convert the aldehydo-acetal of equation II to the hydroxy-acetal in good yield.

However, treatment of **1** or **2** with this reagent afforded a complex mixture of products, as indeed did use of lithium borohydride, lithium aluminium hydride or DIBAL-H (at low temperatures).

Interestingly, Remers and co-workers [6], in an elegant piece of work, had converted the pyrroloindole of equation III to the corresponding hydroxymethyl derivative through the use of diborane and had shown that sodium borohydride treatment of the same pyrroloindole led to the initial reduction of the 2-keto group.

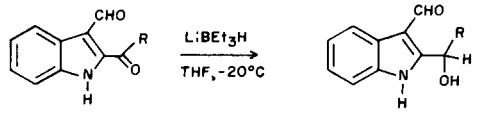
Extrapolation of these results to the problem outlined earlier followed: Lithium triethylborohydride treatment of a variety of 2-acyl-1*H*-indole-3-carboxaldehydes at −20° in tetrahydrofuran led to the formation of indol-2-yl carbinols in good yield (Table I).

However, we encountered problems with selectivity when attempting to use diborane as reagent for conversion of some of our intermediates to the 3-hydroxymethyl derivatives. Consequently, a different approach to the problem was required.

It was reasoned that if the reduction of the 2-acyl-1*H*-indole-3-carboxaldehydes could be carried out under acidic conditions, the aldehyde function could be reduced under kinetic control. This expectation was fully realised in practice.

Thus, when **2** was treated with one equivalent of sodium cyanoborohydride [7] in methanol at *p*H 4, the methyl ether **2a** was rapidly produced in excellent yield. Reduction with two equivalents of sodium cyanoborohydride afforded a high yield of the skatole **2b**. Subsequent treatment of **2** with one equivalent of sodium cyanoborohydride in acetic acid afforded the 3-hydroxymethyl derivative **2c** in good yield.

Table I

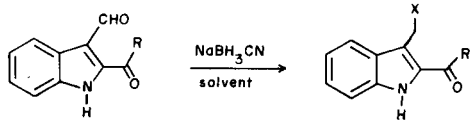


Compound No.		Yield (%)
1	R = CH_3	50
2	R = C_6H_5	85
3	R = 1-(Phenylmethyl)-4-piperidinyl	75

Exposure of other 2-acyl-1*H*-indole-3-carboxaldehydes to these conditions (Table II) also resulted in conversion to the 3-hydroxymethyl derivatives, showing the procedure to hold promise as a general and selective one [8].

In addition, the conversion of the 2-keto function to the indole-2-yl carbinol, under mild conditions, might find application in the production of compounds designed as intermediates for the synthesis of the "dimeric" indole alkaloids [9].

Table II



a) Solvent - methanol; 1 equivalent of sodium cyanoborohydride

Compound No.			Yield (%)
1	R = CH_3	X = OCH_3	90
2	R = C_6H_5	X = OCH_3	92
4	R = 1-(Acetyl)-4-piperidinyl	X = OCH_3	64 + 25 3-hydroxymethyl

b) Solvent - methanol; 2.5 equivalents of sodium cyanoborohydride

2	R = C_6H_5	X = H	84

c) Solvent - acetic acid, 1.0 equivalent of sodium cyanoborohydride

1	R = CH_3	X = OH	88
2	R = C_6H_5	X = OH	92
3	R = 1-(Phenylmethyl)-4-piperidinyl	X = OH	90
4	R = 1-(Acetyl)-4-piperidinyl	X = OH	87

EXPERIMENTAL

General.

All reactions were run under a positive pressure of dry nitrogen except where stated. Infrared spectra were obtained as either solution in the indicated solvent, liquid film or nujol mull on a Perkin Elmer 297 spectrophotometer and are given in cm^{-1}. The nmr spectra were determined in the indicated solvent on a Perkin Elmer R32 or a Bruker spectrometer at 60 or 90 MHz; chemical shifts are given in ppm from tetramethylsilane. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Coupling constants are given in hertz. Mass spectra were taken on an AEI S902 high resolution mass spectrometer at an ionising voltage of 70 eV and an ionising current of 100 mA. Melting points were obtained on a Reichert hot stage and are uncorrected. For column chromatography 'E Merck' Kieselgel G was used except where indicated. Thin layer and preparative thick layer (1 mm) plates were made of E Merck Kieselgel GF254 and activated by drying at 130° for 3 hours. Removal of material from thick layer plates was accomplished by washing with methanol, evaporating solvent and taking up the residue in chloroform. In experiments requiring dry solvents, ether and tetrahydrofuran were distilled from lithium aluminium hydride. Apparatus for experiments requiring anhydrous conditions was dried by flaming in a stream of dry nitrogen.

(I) General Procedure for the Synthesis of 2-Hydroxy-1*H*-indole-3-carboxaldehydes.

The 2-acyl-1*H*-indole-3-carboxaldehyde (1.0 mmole) was dissolved in anhydrous tetrahydrofuran in a 3 necked round bottom flask containing a magnetic stirrer, nitrogen inlet and a rubber septum. The solution was cooled to −20° and 1.5 equivalents of lithium triethylborohydride (as a solution in tetrahydrofuran) added *via* a dry syringe. The solution was stirred at −20° for 2.5 hours, allowed to warm to room temperature, and then quenched with water. Dilution of the mixture with ether and separation and drying (magnesium sulfate) of the organic extracts gave the crude 2-hydroxy-1*H*-indole-3-carboxaldehyde. Purification by plc afforded the pure material. The following were obtained as above.

2-(Hydroxyphenylmethyl)-1*H*-indole-3-carboxaldehyde from 2-Benzoyl-1*H*-indole-3-carboxaldehyde (**2**).

This compound was obtained in 85% yield, mp 198-199.5° from ethanol/water; ir (nujol): 3400-3120 (broad O-H), 3190 (N-H) and 1625 cm^{-1} (CHO); nmr (deuteriochloroform/DMSO-d_6): δ 6.4 (1H, s, *H*-C-OH), 7.2-7.6 (9H, m, aromatic H), 8.1-8.2 (1H, br s, N-H), 10.2 (1H, s, C*H*O); ms: 251 (M^+, 100), 233 (15), 232 (12), 204 (67), 105 (17), 77 (19); mw (calculated for $C_{16}H_{13}NO_2$ 251.094623) 251.09525; uv (log ε): 307 (3.89), 267 (3.91) and 248 (4.15) nm.

Anal. Calcd. for $C_{16}H_{13}NO_2$: C, 76.4; H, 5.2; N, 5.6. Found: C, 76.05; H, 5.3; N, 5.75.

2-(1-Hydroxyethyl)-1*H*-indole-3-carboxaldehyde from 2-Acetyl-1*H*-indole-3-carboxaldehyde (**1**).

This compound was obtained in 50% yield as a yellow gum; ir (chloroform): 3420 (N-H), 3400-3150 (broad O-H), and 1650 cm^{-1} (C=O); nmr (deuteriochloroform): δ 1.3 (3H, d, -C*H*$_3$), 5.5 (1H, q, H_3C-C*H*-), 7.1-7.5 (3H, m, aromatic H), 7.6-7.8 (1H, m, indole 7H), 8.1 (1H, br s, -O-*H*), 9.5 (1H, s, N-H), 10.1 (1H, s, -C*H*O); ms: 189 (M^+, 100), 174 (18), 143 (28), 118 (35), 83 (29); mw (calculated for $C_{11}H_{11}NO_2$ 189.078973) 189.07955; uv (log ε): 325 nm and 248 nm.

Anal. Calcd. for $C_{11}H_{11}NO_2 \cdot CH_3OH$: C, 65.15 H, 6.8; N, 6.3. Found: C, 65.45; H, 6.65; N, 6.4.

2-[Hydroxy-{1-(phenylmethyl)-4-piperidinyl}methyl]-1*H*-indole-3-carboxaldehyde from 2-[{1-(Phenylmethyl)-4-piperidinyl}carbonyl-1*H*-indole-3-carboxaldehyde (**3**).

This compound was obtained in 75% yield as a colorless gum; ir (chloroform): 3420 (N-H), 3400-3150 (broad O-H), and 1650 cm^{-1} (C=O); nmr (deuteriochloroform): δ 1.6-2.3 (6H, m, piperidyl H), 2.8-3.2 (3H, m, piperidyl H), 3.5 (2H, s, -C*H*$_2$Ph), 5.5 (1H, d, *H*-C-OH), 7.05-7.4 (9H, m, aromatic H), 9.5 (1H, br s, N-H), 10.3 (1H, s, C*H*O); ms: 348 (M^+, 5), 330 (1), 172 (100), 146 (18), 91 (100); mw (calculated for $C_{22}H_{24}N_2O_2$ 348.183768) 348.18427.

Anal. Calcd. for $C_{22}H_{24}N_2O_2$: C, 75.9; H, 6.9; N, 8.0. Found: C, 75.55; H, 7.2; N, 7.7.

(II) General Procedure for the Synthesis of 3-Hydroxymethyl-1*H*-indol-2-yl Ketones.

The 2-acyl-1*H*-indole-3-carboxaldehyde (100 mmoles) was dissolved in glacial acetic acid (10 ml) and sodium cyanoborohydride (100 mmoles) added in one portion with stirring. The solution was stirred at room temperature for a further 30 minutes and then worked up. The acetic acid was removed *in vacuo* and the residue taken up in chloroform. The chloroform solution was washed sequentially with 2*N* sodium bicarbonate, water, and saturated sodium chloride, and then dried (magnesium sulfate). Evaporation of the volatiles *in vacuo* afforded the slightly impure 3-hydroxymethylindol-2-yl ketone. Chromatography on 40 g of Kieselgel G (chloroform as eluant) provided pure material. The following were obtained as above.

1-Acetyl-4-[(3-hydroxymethyl)-1*H*-indole-3-ylcarbonyl]piperidine (**4c**) from 1-Acetyl-4-[(3-formyl-1*H*-indole-2-ylcarbonyl]piperidine (**4**).

This compound was obtained in 87% yield, mp 173-174° from ethan-

ol/water; ir (chloroform): 3420 (N-H), 3300 (broad O-H), and 1630 cm^{-1} (broad C=O, amide and ketone); nmr (deuteriochloroform): δ 1.5-2.2 (4H, m, piperidyl H), 2.1 (3H, s, $-CH_3$), 2.7-4.6 (5H, m, piperidyl H), 5.05 (2H, s, $-CH_2OH$), 7.15-7.5 (3H, m, aromatic H), 7.7-7.8 (1H, s, indole 7H), 9.1 (1H, br s, N-H); ms: 300 (M^+, 7), 196 (47), 184 (51), 158 (29), 130 (29), 129 (20), 128 (35), 82 (78), 55 (69), 43 (100); mw (calculated for $C_{17}H_{20}N_2O_3$ 300.147383) 300.14671; uv: (log ε) 317 (4.14) and 240 (4.06) nm.

Anal. Calcd. for $C_{17}H_{20}N_2O_3$: C, 68.0; H, 6.7; N, 9.3. Found: C, 68.1; H, 6.5; N, 9.4.

[3-(Hydroxymethyl)-1*H*-indole-2-yl] Phenyl Ketone (**2c**) from 2-Benzoyl-1*H*-indole-3-carboxaldehyde (**2**).

This compound was obtained in 92% yield, mp 204-207° from ethanol; ir (nujol): 3500-3200 (broad O-H), 3300 (N-H) and 1620 cm^{-1} (C=O); nmr (deuteriochloroform/DMSO-d_6): δ 4.8 (2H, s, CH_2OH), 7.3-7.9 (9H, m, aromatic H), 10.7 (1H, br s, N-H); ms: 251 (M^+, 100), 234 (15), 233 (13), 204 (47), 132 (14), 105 (41), 77 (41); mw (calculated for $C_{16}H_{13}NO_2$ 251.094623) 251.09501; uv (log ε): 328 (4.22) and 252 (4.18) nm.

Anal. Calcd. for $C_{16}H_{13}NO_2$: C, 76.4; H, 5.2; N, 5.6. Found: C, 76.15; H, 5.4; N, 5.6.

1-[3-(Hydroxymethyl)-1*H*-indole-2-yl] Ethanone (**1c**) from 2-Acetyl-1*H*-indole-3-carboxaldehyde (**1**).

This compound was obtained in 88% yield, mp 143-145° from ethanol; ir (nujol): 3500-3100 (broad O-H), 3310 (N-H) and 1640 cm^{-1} (C=O); nmr (deuteriochloroform/DMSO-d_6): δ 2.7 (2H, s, CO*Me*), 5.0 (2H, s, $-CH_2OH$), 7.0-7.5 (3H, m, aromatic H), 7.7-7.8 (1H, m, indole 7H), 10.4 (1H, br s, N-*H*); ms: 189 (M^+, 96), 171 (22), 170 (23), 160 (41), 143 (88), 130 (36), 129 (24), 128 (38), 118 (83), 117 (40), 116 (35), 115 (34), 108 (40), 89 (49), 77 (95), 51 (84), 43 (100); mw (calculated for $C_{11}H_{11}NO_2$ 189.078973) 189.07792; uv (log ε): 314 (4.28) and 239 (4.16) nm.

Anal. Calcd. for $C_{11}H_{11}NO_2$: C, 69.8; H, 5.95; N, 7.4. Found: C, 69.45; H, 5.95; N, 7.4.

[3-(Hydroxymethyl)-1*H*-indol-2-yl][1-phenylmethyl-4-piperidinyl]methanone (**3c**) from 2-[{1-(Phenylmethyl)-4-piperidinyl}carbonyl]-1*H*-indole-3-carboxaldehyde (**3**).

This compound was obtained in 90% yield, mp 190-192.5° from ethanol/water; ir (chloroform): 3500 (broad O-H), 3300 (N-H), 1640 cm^{-1} (C=O); nmr (deuteriochloroform): δ 1.6-2.3 (6H, m, piperidyl H), 2.7-3.1 (3H, m, piperidyl H), 3.5 (2H, s, $-CH_2Ph$), 4.4 (1H, br s, O-H), 5.05 (2H, s, $-CH_2OH$), 7.0-7.6 (9H, m, aromatic H), 9.8 (1H, br s, N-H); ms: 348 (M^+, 10), 330 (15), 172 (56), 146 (39), 91 (100); mw (calculated for $C_{22}H_{24}N_2O_2$ 348.183768) 348.18324; uv (log ε): 315 (4.29) and 241 (4.29) nm.

Anal. Calcd. for $C_{22}H_{24}N_2O_2$: C, 75.9; H, 6.9; N, 8.0. Found: C, 75.8; H, 7.2; N, 7.95.

(III) General Procedure for the Synthesis of 3-(Methoxymethyl)-1*H*-indol-2-yl Ketones.

The 3-aldehydoindol-2-yl ketone (1.0 mmole) was dissolved in anhydrous methanol (10 ml) containing 2 drops of methyl orange. Hydrochloric acid (2*N*) in methanol was added dropwise until the *p*H of the solution was approximately 3. Sodium cyanoborohydride (1.0 mmole) was added in one portion and the mixture stirred at room temperature for 10 hours. At the end of this time the methanol was evaporated and the residue treated with a few drops of 2*N* sulfuric acid. Chloroform (10 ml) and water (5 ml) were added and the mixture transferred to a separating funnel. The chloroform layer was separated and the aqueous layer washed with 2 further 10 ml portions of chloroform. The combined chloroform layers were washed with saturated sodium chloride solution and dried (magnesium sulfate). Evaporation of the solvent afforded the crude methyl ether. Column chromatography (Kieselgel G, 40 g, dichloromethane) afforded the pure crystalline material. The following were obtained as above.

1-[3-(Methoxymethyl)-1*H*-indol-2-yl] Ethanone (**1a**) from 2-Acetyl-1*H*-indole-3-carboxaldehyde (**1**).

This compound was obtained in 90% yield, mp 125-127° from carbon tetrachloride/60-80° petrol; ir (chloroform): 3450 (N-H), 1650 cm^{-1} (C=O); nmr (deuteriochloroform): δ 2.7 (3H, s, $COCH_3$), 3.4 (3H, s, $-OCH_3$), 4.9 (2H, s, $-CH_2O-$), 7.1-7.5 (3H, m, aromatic H), 7.75-7.9 (1H, m, indole 7H), 9.5 (1H, br s, N-H); ms: 203 (M^+, 100), 188 (82), 172 (53), 130 (34), 43 (41); mw (calculated for $C_{12}H_{13}NO_2$ 203.094623) 203.09486; uv (log ε): 313 (4.26) and 236 (4.11) nm.

Anal. Calcd. for $C_{12}H_{13}NO_2$: C, 70.9; H, 6.4; N, 6.9. Found: C, 70.6; H, 6.35; N, 6.85.

[3-(Methoxymethyl)-1*H*-indole-2-yl] Phenyl Ketone (**2a**) from 2-Benzoyl-1*H*-indole-3-carboxaldehyde (**2**).

This compound was obtained in 92% yield, mp 128-129° from carbon tetrachloride/60-80° petrol; ir (chloroform): 3450 (N-H) and 1630 cm^{-1} (C=O); nmr (deuteriochloroform): δ 3.25 (3H, s, $-O-CH_3$), 4.5 (2H, s, $-CH_2OMe$), 7.1-7.65 (3H, m, aromatic H), 7.8-7.95 (1H, m, indole 7H), 9.5 (1H, br s, N-H); ms: 265 (M^+, 100), 250 (49), 232 (30), 204 (23), 105, (30), 77 (37); mw (calculated for $C_{17}H_{15}NO_2$ 265.110272) 265.10955; uv (log ε): 325 (4.17) and 250 (4.16) nm.

Anal. Calcd. for $C_{17}H_{15}NO_2$: C, 77.0; H, 5.7; N, 5.3. Found: C, 76.55; H, 5.85; N, 5.15.

1-Acetyl-4-[{3-(methoxymethyl)-1*H*-indol-2-yl}carboxyl]piperidine (**4a**) from 1-Acetyl-4-[(3-formyl-1*H*-indol-3-yl)carbonyl]piperidine (**4**).

This compound was obtained in 64% yield, mp 201-203° from methanol/ether; ir (chloroform): 3420 (N-H) and 1630 cm^{-1} (C=O, amide and ketone); nmr (deuteriochloroform): δ 1.6-2.15 (4H, m, piperidyl Hs), 2.1 (3H, s, $-CH_3$, amide), 2.6-4.0 (4H, m, piperidyl H), 3.4 (3H, s, $-O-CH_3$), 4.6 (1H, m, piperidyl H), 4.9 (2H, s, $-CH_2-OMe$), 7.05-7.5 (3H, m, aromatic H); ms: 314 (M^+, 82), 282 (21), 239 (19), 196 (100), 184 (70), 160 (53), 156 (19), 130 (30), 129 (35), 128 (25), 43 (46); mw (calculated for $C_{18}H_{22}N_2O_3$ 314.163032), 314.16391; uv (log ε): 316 (4.36) and 233 (4.24) nm.

Anal. Calcd. for $C_{18}H_{22}N_2O_3$: C, 68.8; H, 7.0; N, 8.9. Found: C, 69.1; H, 7.25; N, 9.2.

(IV) General Procedure for the Synthesis of 3-Methyl-1*H*-indol-2-yl Ketones.

2-Benzoyl-1*H*-indole-3-carboxaldehyde (**2**) (249 mg, 1.0 mmole) was dissolved in absolute methanol (15 ml) and 157 mg (2.5 mmoles) of sodium cyanoborohydride added in one portion with stirring. A trace of methyl orange was added and 2*N* hydrochloric acid in methanol added to maintain a red colour. The solution was stirred for 4 hours and at the end of this time the methanol was evaporated and the residue suspended in 10 ml of water. Chloroform (20 ml) was added and, after shaking, the resultant chloroform layer was separated. The aqueous layer was extracted with 2 more portions of chloroform (2 × 10 ml) and the combined organic extracts dried (magnesium sulfate) and evaporated to give 200 mg of the crude skatole. Purification by plc gave 197 mg of crystalline compound **2b** (84%), mp 135-138° from 60-80° petrol; ir (chloroform): 3440 (N-H), and 1630 cm^{-1} (C=O); nmr (deuteriochloroform): δ 2.3 (3H, s, $-CH_3$), 7.0-7.85 (9H, m, aromatic H), 8.9 (1H, br s, N-*H*); ms: 235 (M^+, 100), 234 (88), 216 (23), 158 (15), 130 (23), 105 (12), 77 (42); mw (calculated for $C_{16}H_{13}NO$: 235.099708) 235.09946; uv (log ε) 326 (4.19) and 253 (4.30) nm.

Anal. Calcd. for $C_{16}H_{13}NO$: C, 81.7; H, 5.5; N, 5.96. Found: C, 81.9; H, 5.7; N, 5.95.

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