Tetrahedron Vol. 49, No. 42, pp. 9517-9524, 1993
Printed in Great Britain

0040-4020/93 $6.00+.00
Pergamon Press Ltd

Experiments Towards the Total Synthesis of Five-Membered D-Ring Ergot Alkaloid Analogues.

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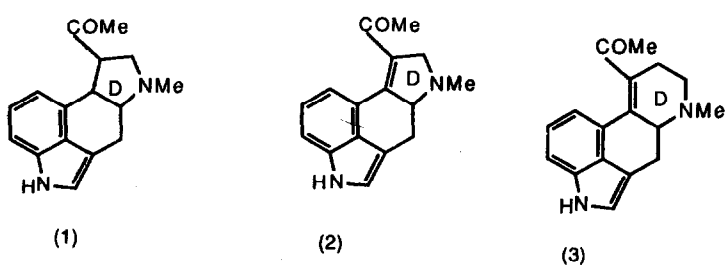
(*Received in UK* 5 *May* 1993; *accepted* 6 *August* 1993)

Abstract: The known tricyclic ketone, Kornfeld's ketone (**5**)[1], has been prepared in a much improved yield by modification of the usual procedure from the commercially available indole-3-propionic acid. Direct condensation with *N*-methylaminopropionitrile yielded a derivative, 4-(*N*-methyl-*N*-2'-cyanoethyl)amino-1-benzoyl-2,2a,3,4-tetrahydrobenz[cd]indol-5H-(1H)-one which could not be cyclized to the desired five-membered D-ring ergot analogue. In a different approach the 4-methylamino derivative was prepared *via* the carbamate and the corresponding oxazolinone. However, introduction of the requisite side-chain for the construction of the D-ring failed. Finally in the presence of an amide substituent at C-4 of the tricyclic ketone two five-membered D-ring analogues were obtained under Cope's reaction conditions by introducing a two-carbon chain at C-5.

INTRODUCTION

The objective of this investigation was to carry out a total synthesis of five-membered D-ring ergot analogues, starting from the commercially available indole-3-propionic acid. It was hoped to prepare compound (**1**) in which the D-ring is saturated and also the unsaturated D-ring analogue (**2**) in which a double bond is introduced at 9a,9 position and while attempting to do these to preserve the stereochemistry of the ergoline structure. It is not difficult to visualize the similarity in stereochemistry between the lysergic acid diethylamide (**3**), LSD, and the proposed series.

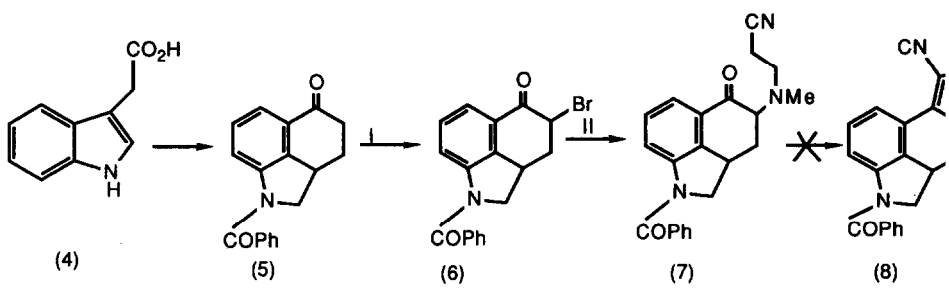


(fig. 1)

RESULTS AND DISCUSSION

As a Starting point in the design of the five-membered D-ring ergot analogues, two kno syntheses of natural ergolines were considered[1,2,3]. The known indoline tricylic ketone (5) was because of its presumed greater stability over the corresponding indole compound[1]. The ketone obtained in a very much improved yield in four steps by modifications of the known method from 3-propionic acid[1]. The complete spectral data are now given as only the u.v. and i.r. data are a in the literature. The bromo-derivative (6) was obtained in good yield by using trimethylphenylamr tribromide. Reaction of (6) with *N*-methylaminopropionitrile in boiling benzene for 3 hours yiel required aminoketone (7) in about 50% yield. The presence of an activated methylene g compound (7) suggested that cyclization to the five-membered D-ring analogue might be induce formation of a nitrile-stabilized carbanion which would then condense on the C-5 carbonyl grou hoped that (8) could then be obtained. The nitrile function could then be utilized in the prepar various derivatives. However, all attempts in this direction proved unsuccessful as shown below (1):

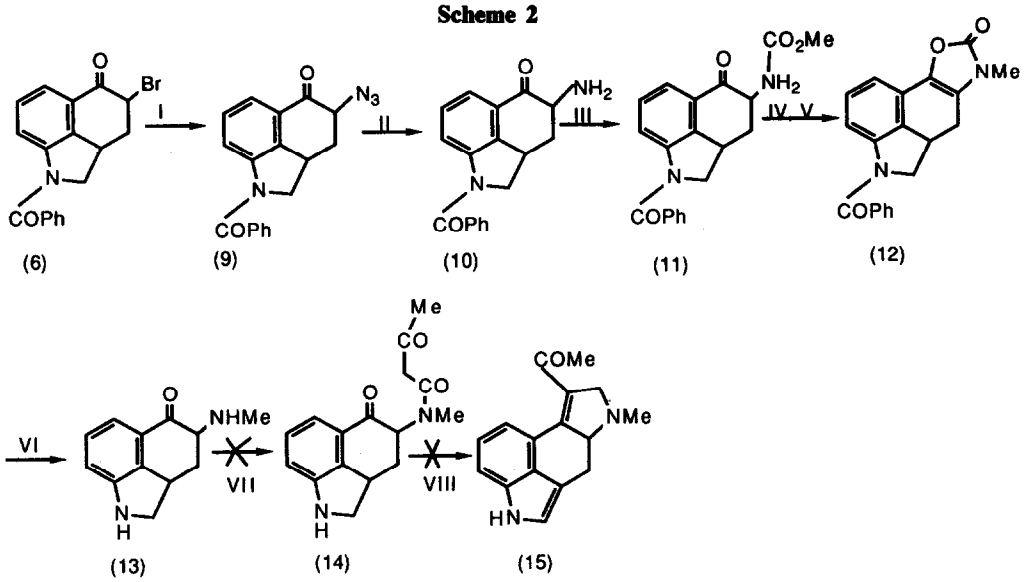
Scheme 1



I. $PhN(CH_3)_3Br.Br_2$ II. $CH_3NHCH_2CH_2CN$

In a different approach the methylamino ketone (13) was prepared following the exa Bowman[4] who worked with the indole series. The azido-derivative (9) was obtained from (6) wl reduced to the 4-amino-derivative and isolated as the hydrochloride salt (10). The free base i unstable; direct monomethylation could not be achieved because compound (10) decomposed r the presence of a base. When (9) was allowed to react with methyl chloroformate in the prese base the carbamate (11) was formed which on treatment with sodium hydride followed by meth afforded the crystalline *N*-methyloxazolinone (12). Hydrolysis of (12) in propan-2-ol with conc hydrochloric acid yielded the 4-methylamino derivative (13) (scheme 2). The 1-benzoyl group lost in the process. It was hoped that the condensation of (13) with diketene would afford a prod with an activated methylene group; such a compound could then be cyclized to (15) by treatm a base. The presence of a carbonyl group at C-5 makes such a procedure feasible. All attempt direction failed:

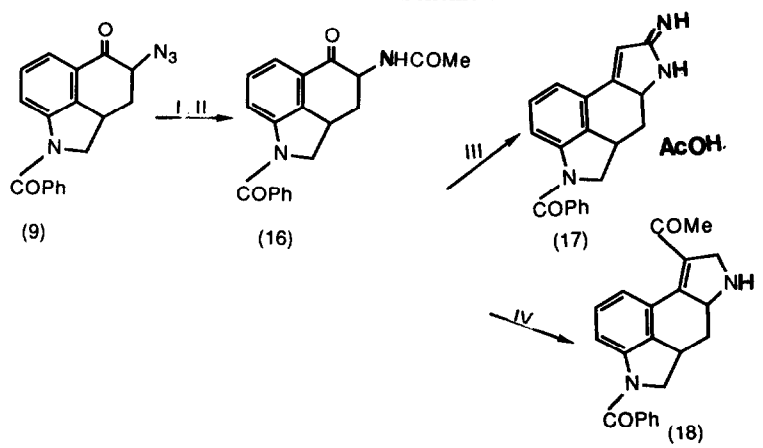
Scheme 2



I. NaN_3 II. H_2/Pd/C III. $NaHCO_3$-$ClCO_2CH_3$ IV. NaH V. CH_3I VI. HCl VII. Diketene VIII. Base.

Finally we directed our efforts at introducing a two-carbon chain at C-5 in the presence of an amide substituent at C-4. Hydrogenation of the azido derivative (**9**) in a mixture containing acetic anhydride gave the acetamido compound (**16**), which is quite stable. It was found that this compound reacted with ethyl cyanoacetate in refluxing toluene in the presence of 15% ammonium acetate in acetic acid in a sequence involving hydrolysis, deacetylation, decarboxylation and ring closure. The product which separated from the mixture at 140° was the tetracyclic salt (**17**). With ethyl acetoacetate, under similar conditions, the amide (**18**), scheme 3, was obtained. At this stage of the investigation all attempts to remove the 1-benzoyl group or to effect further modifications led to extensive decomposition:

Scheme 3



I. H_2/pd II. $(CH_3CO)_2O$ III. $CNCH_2CO_2Et$ IV. $CH_3COCH_2CO_2Et$.

EXPERIMENTAL

Melting points were determined on a Gallenkamp electrically heated block and are uncorrected. IR spectra were recorded in nujol mulls on sodium chloride plates, unless stated otherwise, on a Perkin-Elmer 298 spectrophotometer (V_{max} in cm^{-1}), incorporated with a data station. UV spectra were recorded in the solvent indicated for each compound on a Perkin-Elmer (λ_{max} in nm, ϵ) spectrophotometer, incorporated with a data station. ^{1}HNMR spectra were recorded on a Bruker WM 250 (250 MHz), a Nicolet NT 200 (200 MHz) or a Perkin-Elmer R32 (90 MHz) spectrometer (chemical shift, δ, ppm and J values in Hz). ^{13}CNMR spectra were recorded on a Vg micromass 16F instrument, incorporated with a data system Vg 2000, at 35 and 70 eV.

Thin layer chromatography (TLC) was performed on a Merck 60GF254 pre-coated silica gel plates. The Van-Salkonski spray reagent[5] was used to locate TLC spots for the indole compounds. The cerium (IV) based reagent[6] was used for the indoline compounds. Indoline derivatives showed up as intense red or brown spots without heating. *N*-protected indolines were not made visible under these conditions but required that the plates be gently warmed to produce the characteristic blue spots. Preparative TLC was done with 20 X 20 (0.1 mm thickness) Merck silica gel 60GF 254 plates activated at 110° for 0.5 hours. Column chromatography was conducted with Merck Kieselgel (0.0630 - 0.20 mm grade) silica. Drying and/or purification of organic solvents was done as described by Riddick and Bunger[7].

1-Benzoyl-2,2a,3,4-tetrahydrobenz[cd]indol-5(1H)-one (5)

A mixture of 1-benzoyl-3-(2-carboxyethyl)-2,3-dihydroindole (2.00 g, 7 mmoles) obtained from indole-3-propionic acid[1] and polyphosphoric acid (25.50 g) was stirred at 100° for 2 hours and allowed to cool to room temperature. The dark mixture was poured into a mixture of crushed ice (10.00 g) and water (25 ml) and when all the ice had melted the mixture was extracted with dichloromethane (3 x 25 ml) and water (2 x 50 ml). The extract washed with aqueous sodium bicarbonate solution (2 x 25 ml) and water (2 x 50 ml). It was dried over magnesium sulphate and the solvent removed *in vacuo* to yield a yellow oil which on trituration with cold ether afforded a light yellow solid. This was recrystallized from methanol to give (**5**), yield 1.30 g (69%), m.p. 145 - 146°, (lit. 146 - 147°); UV (acetonitrile): 332 (4,168) 250 (27,142); IR: 1685 (ketone C=O), 1626 (amide C=O), 1582 (C=C, Ar); ^{1}HNMR ($CDCl_3$): 2.00 (1H, ddt, H-3_{ax}, 4.00, 12.00), 2.36 (1H, dt^{br}, H-3_{eq}, 4.00, 12.00), 2.60 (1H, dt, H-4_{ax}, 4.00, 12.00), 2.75 (1H, dt, H-4_{eq}, 4.00, 12.00), 3.65 (1H, m, H-2a), 3.80 (1H, t, H-2_{ax}, 10.00, 20.00), 4.40 (1H, m^{br}, H-2_{eq}), 7.36 - 7.60 (8H, m, Ar); ^{13}CNMR ($CDCl_3$): 28.49 (1C, t, C-3), 37.70 (1C, d, C-2a), 38.44 (1C, t, C-4), 57.85 (1C, t, C-2), 121.34 - 141.84 (12C, m, Ar), 168.98 (1C, s, amide C), 196.33 (1C, t, ketone C); MS: m/e 277 (42) (M^+), 105 (100) ($PhCO^+$), 77 (3%) (Ph^+).

Found C, 77.55; H, 5.42; N, 4.95 $C_{18}H_{15}NO_2$ requires C, 77.95; H, 5.45; N, 4.95%.

1-Benzoyl-4-bromo-2,2a,3,4-tetrahydrobenz[cd]indol-5(1H)-one (6)

A solution of trimethylphenylammonium tribromide (13.60 g, 36 mmoles) in tetrahydrofuran (50 ml) was added to an ice-cold solution of (**5**) (10.00 g, 36 mmoles) in tetrahydrofuran (100 ml), and stirred at 0° for 0.5 hours. The mixture was filtered and the red filtrate evaporated *in vacuo* to dryness to yield a light yellow solid. The product was crystallized from acetonitrile to afford (**6**), yield 10.40 g (81%), m.p. 181 - 182°; UV (acetonitrile): 332 (4,168) 250 (27,142); IR: 1681 (ketone C=O), 1634 (amide C=O),

1588, 1572 (C=C, Ar); ^{1}HNMR ($CDCl_3$): 2.33 (1H, dt, H-3_{ax}, 3.14, 15.70), 2.69 (1H, dt, H-3_{eq}, 3.14, 15.70), 3.80 (1H, t, H-2a), 4.05 (1H, m, H-2_{ax}), 4.48 (1H, m^{br}, H-2_{eq}), 4.68 (1H, t, H-4_{ax}, 3.14, 6.28), 7.40 - 7.60 (8H, m, Ar); ^{13}CNMR ($CDCl_3$): 33.20 (1C, d, C-3), 36.70 (1C, t, C-2a), 48.63 (1C, d, C-4), 57.00 (1C, t, C-2), 121.70 - 142.00 (12C, m, Ar), 169.00 (1C, s, amide C), 188.42 (1C, s, ketone C); MS: m/e 356 (3) (M^+), 277 (10) (M^+ - Br), 105 (100) ($PhCO^+$), 77 (3%) (Ph^+).
Found C, 60.26; H, 3.69; N, 3.90 $C_{18}H_{14}BrNO_2$ requires C, 60.70; H, 4.00; N, 3.80%.

4-(N-Methyl-N-2'-cyanoethyl)amino-1-benzoyl-2,2a,3,4-tetrahydrobenz[cd]indol-5(1H)-one (7).

Method A. 2-*N*-Methylaminopropionitrile (0.66 ml, 7.20 mmoles) was added to suspension of (**6**) (0.50 g, 1.40 mmoles) in benzene (20 ml) and heated under reflux for 3 hours. The mixture was allowed to cool to room temperature and filtered. The filtrate was washed several times with ice-cold water after which it was extracted with cold dilute hydrochloric acid (300 ml), containing the concentrated acid (10 ml). The acid extracts were immediately added to ice-cold 2N sodium hydroxide and extracted with chloroform (3 x 50 ml). The extract was dried over magnesium sulphate, treated with activated carbon, and the solvent removed *in vacuo* to yield an oil which gave an orange solid on trituration with cold ether. It was further purified by column chromatography (ethyl acetate) to give (7), yield 2.25 g (50%), m.p. 241 - 243°.

Method B. A mixture of 2-*N*-methylaminopropionitrile (5), and (**6**) (0.50 g, 1.40 mmoles) was stirred for 24 hours at room temperature. The resulting red solution was poured into a large excess of a mixture of crushed ice and cold water. When all the ice had melted the light-brown solid formed was filtered off, washed repeatedly with cold water and allowed to dry in air. It was dissolved in chloroform and dried over magnesium sulphate, treated with activated carbon and the solvent removed *in vacuo* to yield an oil which afforded (7) as a yellow solid on trituration with ether, yield 0.35 g (69%), m.p. 241 - 2436°, UV (acetonitrile): 400 (1,500), 314 (8,600), 233 (26,955); IR: 2245 (CN), 1687 (ketone C=O), 1642 (amide C=O), 1594 (C=C, Ar); ^{1}HNMR ($CDCl_3$): 2.13 (1H, t, H-3_{ax}, 11.77, 23.53), 2.50 (1H, m, H-3_{eq}), 2.51 (3H, s, NMe), 2.52 (2H, t, N-CH_2), 3.10 (2H, t, CH_2-CN, 7.06, 14.12), 3.60 (1H, dd, H-4, 4.71, 11.77), 3.74 (1H, m, H-2a), 3.88 (1H, t, H-2_{ax}, 11.77, 23.53), 4.40 (1H, m^{br}, H-2_{eq}), 7.26 - 7.63 (8H, m, Ar); MS: m/e 359 (2) (M^+), 302 (35) (M^+ - CH_2CN), 105 (100) ($PhCO^+$), 77 (30%) (Ph^+).
Found C, 73.88; H, 6.04; N, 11.46 $C_{22}H_{21}N_3O_2$ requires C, 73.52; H, 5.89; N, 11.69%.

4-Azido-1-benzoyl-2,2a,3,4-tetrahydrobenz[cd]indol-5(1H)-one (9)

Sodium azide (3.80 g, 56 mmoles) in water (20 ml) was added with stirring and cooling to a solution of (**6**) (10.00 g, 28 mmoles) in dimethylformamide (60 ml) containing acetic acid (4 ml) previously cooled to 0°. Addition of a large excess of water caused the product to precipitate out. The yellow solid was filtered off and washed thoroughly with water. It was crystallized from ethanol, yield 8.20 g (92%), m.p. 146 - 147°, UV (acetonitrile): 332 (5,030), 244 (26,643), 204 (16,744); IR: 2153 (N_3), 1684 (ketone C=O), 1642 (amide C=O), 1589 (C=C, Ar); ^{1}HNMR ($CDCl_3$): 2.02 (1H, t, H-3_{ax}, 11.00, 22.00), 2.60 (1H, m^{br}, H-3_{eq}), 3.69 (1H, m, H-2a, 8.90), 3.80 (1H, t, H-2_{ax}, 8.90, 17.70), 4.33 (1H, dd, H-4, 4.45, 13.32), 4.43 (1H, m^{br}, H-2_{eq}), 7.29 - 7.62 (8H, m, Ar); ^{13}CNMR ($CDCl_3$): 35.34 (1C, t, C-3), 35.67 (1C, 2d, C-2a), 57.52 (1C, t, C-2), 64.80 (1C, d, C-4), 122.02 - 142.02 (12C, m, Ar), 168.71 (1C, s, amide C), 192.71 (1C, s, ketone C); MS: m/e 290 (6) (M^+ - N_2), 277 (2) (M^+ - N_3), 105 (100) ($PhCO^+$), 77 (35%)

(Ph^+).
Found C, 67.57; H, 4.63; N, 17.33 $C_{18}H_{14}N_4O_2$ requires C, 67.90; H, 4.40; N, 17.60%.

4-Amino-1-benzoyl-2,2a,3,4-tetrahydrobenz[cd]indol-5(1H)-one hydrochloride (10)

A mixture of (**9**) (1.00 g, 3 mmoles) in acetic acid (20 ml) and 10% palladium on activate (0.20 g) was hydrogenated at 60 p.s.i. on a Parr apparatus for 1 hour. The catalyst was filtered o with a little acetic acid. Concentrated hydrochloric acid (2 ml) was added to the filtrate to afford solid which was washed with a little chloroform. It was purified by column chroma (chloroform/methanol 5/1) to yield (**10**), 0.93 g (90%), m.p. 200 - 202°, UV (acetonitrile): 33 332 (6,296), 238 (30,872); IR: 3367 (NH), 2620 ($^+$NH), 1708 (ketone C=O), 1638 (amide C= (C=C, Ar); ^{1}HNMR (DMSO-d_6): 2.17 (1H, dt, H-3_{ax}, 12.50), 2.73 (1H, m, H-3_{eq}, 12.50), 3.88 (1 2a), 3.93 (1H, m, H-2_{ax}), 4.29 (1H, m^{br}, H-2_{eq}), 4.43 (1H, d^{br}, H-4), 7.43 - 7.68 (8H, m, Ar), 8.78 NH_2); MS: m/e 292 (2) (M^+ - HCl), 105 (100) ($PhCO^+$), 77 (39%) (Ph^+).
Found C, 65.90; H, 4.89; N, 8.20 $C_{18}H_{17}ClN_2O_2$ requires C, 65.75; H, 4.91; N, 8.52%.

Methyl 1-benzoyl-1,2,2a,3,4,5-hexahydro-5-oxo-benz[cd]indol-4-ylcarbamate (11)

Methyl chloroformate (0.70 ml, 9 mmoles) was added to a stirred suspension of (**10**) mmoles) in dichloromethane (20 ml). Triethylamine (2.11 ml, 15 mmoles) was then added at su that the temperature was kept under 12°. Stirring was continued for 0.25 hours, whereupon wa was added, the cooling bath removed, and the mixture stirred for further 0.5 hours. The org was separated and washed successively with 0.5M hydrochloric acid (3 x 20 ml), saturate bicarbonate solution (3 x 20 ml) and water (3 x 50 ml), and then dried over magnesium sulp solvent was removed *in vacuo* to yield an oil which solidified on trituration with cold eth crystalline urethane (**11**), yield 1.80 g (85%), m.p. 120 - 122°, UV (acetonitrile): 300 (6,307), 238 208 (18,569); IR: 3317 (NH), 1685 (C=O), 1589 (C=C, Ar); ^{1}HNMR (DMSO-d_6): 2.11 (1H, 12.50, 25.00), 2.34 (1H, m^{br}, H-3_{eq}), 3.55 (3H, s, OMe), 3.72 (1H, m^{br}, H-2a), 3.90 (1H, m^{br}, H (1H, m^{br}, H-2_{eq}), 4.40 (1H, dt, H-4, 6.25, 12.50), 7.38 - 7.66 (8H, m, Ar), 8.08 (2H, d^{br}, NH_2); 350 (4) (M^+), 318 (2) (M^+ - MeOH), 105 (100) ($PhCO^+$), 77 (31%) (Ph^+).
Found C, 68.20; H, 5.10; N, 7.80 $C_{20}H_{18}ClN_2O_4$ requires C, 68.56; H, 5.18; N, 8.00%.

4,5,5a,6,7,8-Hexahydro-4-benzoyl-7-methylindol[3,4-fg]benzoxazolin-8-one (12)

A solution of (**11**) (0.50 g, 1.40 mmoles) in dimethylformamide (20 ml) was added v torque stirring to a suspension of sodium hydride (0.114 g, 8.50 mmoles) in dimethylformamid and the mixture, which had become semi-solid, kept at 40 - 50° for 0.5 hours; methyl iodide v with cooling and the mixture stirred at room temperature until neutral. The solvent was remove (bath temperature 100°). Addition of water afforded the light-brown product (**12**), yield 0.40 m.p. 222 - 224°, UV (acetonitrile): 303 (13,992), 258 (17,049), 211 (14,291); IR: 1760 (oxazolinc (amide C=O), 1601,1576 (C=C, Ar); ^{1}HNMR (DMSO-d_6): 2.64 (1H, m, H-3_{ax}, 12.50, 25.00), m^{br}, H-3_{eq}), 3.16 (3H, s, NMe), 3.74 (1H, m^{br}, H-2a), 3.93 (1H, m^{br}, H-2_{ax}), 4.24 (1H, m^{br}, H-2 7.61 (8H, m, Ar); MS: m/e 332 (25) (M^+), 105 (100) ($PhCO^+$), 77 (3%) (Ph^+).
Found C, 72.20; H, 4.96; N, 8.23 $C_{20}H_{16}ClN_2O_3$ requires C, 72.28; H, 4.85; N, 8.43%.

4-Methylamino-2,2a,3,4-tetrahydrobenz[cd]indol-5(1H)-one hydrochloride (13)

Compound (**12**) (0.40 g, 1.2 mmoles) was boiled with propan-2-ol/concentrated hydrochloric acid, 2/1, (10 ml) for 2 hours during which time the colour went from light-brown to dark green. The mixture was treated with activated carbon and filtered to yield a green solution. The solvents were removed *in vacuo* and the residual gum boiled with acetone (5 ml) when the product, (**13**), crystallized, yield 0.18 g (62%), m.p. 240 - 244°, UV (acetonitrile): 366 (4,965), 332 (4,679), 248 (19,717), 210 (11,649); IR: 3317 (NH), 1685 (ketone C=O), 1589 (C=C, Ar); ^{1}HNMR (DMSO-d_6): 2.21 (1H, dt, H-3_{ax}, 12.50, 25.00), 2.63 (3H, s, NMe), 2.75 (1H, m, H-3_{eq}, 5.00, 12.50), 3.34 (1H, t, H-2_{ax}, 10.00, 20.00), 3.76 (1H, m, H-2a, 5.00, 10.00), 3.96(1H, t, H-2_{eq}, 10.00, 20.00), 4.52 (1H, d^{br}, H-4), 7.28 - 7.48 (3H, m, Ar), 9.50 (1H, br, NH); MS: m/e 202 (42) (M^+ - HCl), 171 (100) (M^+ - HCl - NH_2Me).

Found C, 60.10; H, 6.32; N, 11.63 $C_{12}H_{15}ClN_2O$ requires C, 60.38; H, 6.33; N, 11.74%.

4-Acetamido-1-benzoyl-2,2a,3,4-tetrahydrobenz[cd]indol-5(1H)-one (16)

10% Palladium on activated carbon (1.00 g) was added to a suspension of (**9**) (5.00 g, 16 mmoles) in acetic acid containing acetic anhydride (1.90 ml, 25 mmoles). The mixture was hydrogenated on a Parr apparatus at 20 p.s.i. The reaction took 6 hours to go to completion, after which the catalyst was filtered off and washed with a little acetic acid. The green solution was evaporated to a small volume and then taken up in ethyl acetate (25 ml). Water (50 ml) was added and the mixture was separated. The aqueous layer was further extracted with ethyl acetate (2 x 25 ml). The combined organic extracts were washed thoroughly with water (3 x 50 ml) and dried over magnesium sulphate. The solvent was removed *in vacuo* to yield a yellow solid. A pure sample was obtained by dissolving the crude product in acetone and allowing the solution to stand at room temperature. Crystals began to appear after 0.5 hours. Altternatively the crude yellow solid was purified by column chromatography, chloroform/methanol, 5/1. The average yield of (**16**) was 4.50 g (88%), m.p. 165 - 166°, UV (acetonitrile): 330 (5,149), 238 (24,308), 205 (16,150); IR: 3300 (NH), 1680 (ketone C=O), 1640 (amide C=O), 1590 (C=C, Ar); ^{1}HNMR ($CDCl_3$): 1.80 (1H, dt, H-3_{ax}, 12.50, 25.00), 2.10 (3H, s, OMe), 3.30 (1H, m^{br}, H-3_{eq}), 3.73 (1H, t, H-2a, 12.50, 25.00) 3.84 (1H, m, H-2_{ax}), 4.40 (1H, m^{br}, H-2_{eq}), 4.66 (1H, dt, H-4, 5.00, 10.00), 6.55 (1H, d, NH, 5.00), 7.45 - 7.63 (8H, m, Ar); ^{13}CNMR ($CDCl_3$): 22.90 (1C, q, CH_3), 35.49 (1C, t, C-3), 36.60 (1C, d, C-2a), 56.01 (1C, t, C-2), 57.25 (1C, d, C-4), 121.83 - 142.13 (12C, m, Ar), 168.80 (1C, s, 2° amide C), 170.48 (1C, s, 3° amide), 194.00 (1C, s, ketone C); MS: m/e 334 (21) (M^+), 276 (2) (M^+ - $NHCOCH_3$), 105 (100) ($PhCO^+$), 77 (28%) (Ph^+).

Found C, 71.51; H, 5.50; N, 8.26 $C_{20}H_{18}N_2O_2$ requires C, 71.80; H, 5.40; N, 8.38%.

4-Benzoyl-5,5a,6,6a,7,8-hexahydro-8-imino-4H-indolo[6,5,4-cd]indolinium acetate (17)

A mixture of (**16**) (0.50 g, 1.50 mmoles), ethyl cyanoacetate (1.35 g, 12 mmoles), 15% ammonium acetate in acetic acid (0.83 ml) and toluene (10 ml) was heated under reflux. A clear solution resulted after 0.25 hours, and 2 hours later the solution was evaporated to a small volume when a yellow solid precipitated. It was purified by column chromatography, ethyl acetate/methanol, 5/1, to give (**17**), yield, 0.45 g (80%), m.p. 230 - 233°, IR: 3300 (NH), 2900 (OH), 1660 (C=O), 1630 (amide C=O), 1600 (C=C, Ar); ^{1}HNMR ($CDCl_3$): 1.80 (3H, s, MeCOO), 2.40 (1H, m, H-6_{ax}), 2.75 (1H, m, H-6_{eq}), 3.70 (1H, m, H-5), 3.91 (1H, m, H-5_{ax}), 4.50 (1H, br, H-5_{eq}), 6.50 (1H, s, C-H), 7.01 - 7.62 (8H, m, Ar), 8.50 (2H, br, NH) 12.01 (1H, br, COOH); MS: m/e 315 (68) (M^+ - AcOH), 210 (23) (M^+ - COPh - AcOH), 105 (100) ($PhCO^+$), 77 (40%) (Ph^+).

Found C, 63.89; H, 4.45; N, 10.84 $C_{22}H_{21}N_3O_5$ requires C, 63.90; H, 4.56; N, 11.19%.

9-Acetyl-4-benzoyl-5,5a,6,6a-tetrahydro-4H-indolo-[6,5,4-cd]indole-8-one (18)

A mixture of (**16**) (0.20 g, 0.60 mmoles), ethyl acetoacetate (1.56 g, 12 mmoles), 15% ammonium acetate in acetic acid (2 ml) and toluene (10 ml) was heated under reflux for 1 hour. The solution formed was evaporated *in vacuo* until crystals began to appear. The mixture was left to stand at 0° and when crystallization was complete the yellow crystals were filtered off, yield, 0.16 g (64%), m.p. 280 - 283°, IR: 3300, 3200 (NH), 1695 (ketone C=O), 1630 (amide C=O), 1595 (C=C, Ar); ^{1}HNMR ($CDCl_3$): 2.41 (3H, s, COMe), 2.70 (1H, t, H-6_{ax}), 3.04 (1H, m, H-6_{eq}), 3.85 (1H, m, H-5), 3.95 (1H, m, H-5_{ax}), 4.50 (1H, br, H-5_{eq}), 7.00 - 7.60 (8H, m, Ar), 8.07 (1H, d, NH); MS: m/e 315 (100) (M^+ - COMe), 210 (33) (M^+ - COPh - COMe), 105 (48) ($PhCO^+$), 77 (40) (Ph^+), 43 (2%) ($MeCO^+$).
Found C, 73.22; H, 4.85; N, 7.55 $C_{22}H_{18}N_2O_3$ requires C, 73.70; H, 5.01; N, 7.81%.

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ACKNOWLEDGEMENT

The author wishes to thank the Head and the technical staff of Chelsea Department of Pharmacy, King's College, University of London, where most of the work was done. The guidance provided by Professor G.V. Boyd of the Department of Organic Chemistry, The Hebrew University of Jerusalem, Givat Ram, Israel, is also appreciated.