Synthesis of N-benzylsecodine

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Summary: A short synthetic route to N-benzylsecodine is described involving a Friedel-Crafts acylation at the indole 2- position followed by a Wittig reaction to generate the acrylate moiety.

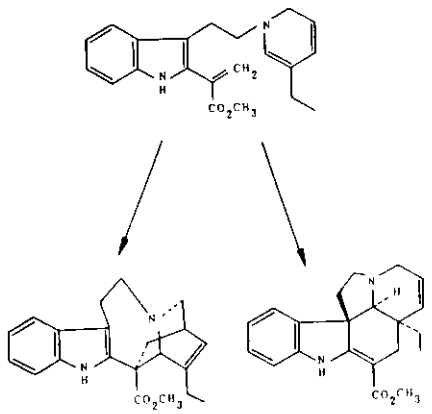
Introduction

1,2-Dihydropyridines play an important role in the biosynthesis of indole alkaloids[1,2]. Scott proposed the achiral acrylic ester dehydrosecodine to account for the in vivo synthesis of aspidosperma and iboga alkaloids (Scheme I)[3]. In view of the central importance of dehydrosecodine, a number of attempts have been made to synthesize and use it for the synthesis of the above alkaloids[4-9]. A new synthetic approach toward controlled selective synthesis of catharanthine and tabersonine derivatives in high yield via 15-oxosecodine intermediates has recently been reported by Kuehne et. al.,[12] while Atta-ur-Rahman et. al.,[11] have also reported a short route towards the synthesis of N-methyl secodine in high yield. It was thought worthwhile to prepare N- benzylsecodine by an analogous route, which on oxidation and intramolecular Diels-Alder reaction might afford either the catharanthine or tabersonine derivatives. N-Benzyldehydrosecodine has previously been converted to N-benzyl derivatives of catharanthine, carbomethoxycleavamine and vincadifformine, in low yields by rather long routes[10]. The synthesis of N-benzylsecodine described here is short, based on a facile Friedel-Craft's acylation at the indole-2-position which is followed by a Wittig reaction (Scheme II).

N-Benzyl indole acetic acid(2) was prepared in good yields (80%) by benzylation of indole acetic acid (1) (NaH, $C_6H_5CH_2Cl$, THF, reflux 12 hours). It is interesting that N-benzylation was not achieved when the reaction was carried out at room temperature even for a period of 100 hours, in contrast to the methylation of indole acetic acid[11]. The product was esterified to the corresponding methyl ester (3) in 80% yield (MeOH, H_2SO_4, 24 hours, 25°C). It was found that the amount of acid was a critical factor in the esterification, as an excess of acid resulted in significant lowering of the yields of the ester. Reduction (LAH, ether, 24 hours, 25°C) gave the alcohol (4) which was converted to the corresponding bromide (5) smoothly (PBr_3, reflux in benzene, 2 hrs). N-Benzyltryptophyl bromide and 3-ethyl pyridine were than heated in a sealed tube at 120°C to afford the corresponding quaternary salt, N-benzyl-3β(-3-ethyl-pyridinium) ethyl indole (6). Reduction of the salt with sodium borohydride in the presence of triethyl amine afforded the tetrahydropyridine derivative (7).

Friedel-Craft's acylation of (7) was carried out using monomethyl oxalyl chloride and $AlCl_3$. Strictly anhydrous conditions and pre- drying of

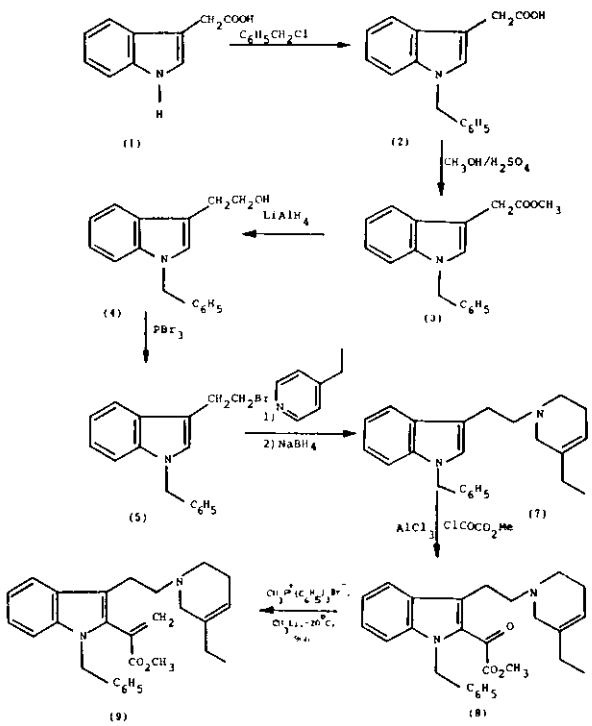
aluminium chloride under high vacuum were necessary for the smooth acylation, otherwise the acylation proceeded in low yields. When pre-dried aluminium chloride was not used, chlorination was observed and a chloro product was obtained (10). This product was characterised by its mass spectrum and its fragmentation pattern.



Scheme 1

Friedel-Craft's acylation of the tetrahydropyridine derivative (7) was found to afford mainly the 2-acyl indole (60% yield) along with a second minor product. The 2-acyl indole (8) was characterized by its UV spectrum which was typical of 2-acyl indoles and was similar to N-methyl-2-pyruvoyl-3β (1,2,5,6) ethyl- tetrahydropyridyl)-ethyl indole,[11] showing absorption maxima at 206, 245 and 323 nm and minima at 230 and 270 nm. The IR spectrum exhibited carbonyl absorptions at 1735 cm^{-1} and 1640 cm^{-1} corresponding to ester carbonyl and keto functions respectively. The high resolution mass spectrum afforded the parent ion peak at m/z 430, consistent with the molecular formula $C_{27}H_{30}N_2O_3$. The ^{1}H- NMR showed the presence of a sharp singlet at δ 4.0 for the O-methyl protons.

The Wittig reaction was then carried out by using methylene triphenylphosphonium bromide for introducing the α-methylene function. This was achieved by carrying out the reaction with (8) at low temperature (-20°C) for 96 hrs, which afforded N-benzyl secodine (9) in 15% yield.The UV spectrum of (9) showed absorption maxima at 275, 295 nm and minima at 260, 280 nm. This is characteristic of the indole-2-acrylic ester system. The mass spectrum was consistent with the structure (M^+-428). The ^{1}H-NMR showed two characteristic



Scheme 2

doublets at δ 6.45 and δ 6.9 for C-17Ha, and C-17Hb protons respectively which confirmed the formation of the product (9).

Experimental

Mass spectra were recorded on Finnigan MAT-312 mass spectrometer connected to PDP 11/34 (DEC) computer system. The ultraviolet spectra were recorded on a Shimadzu UV-240 spectrophotometer. The infrared spectra were recorded on JASCO A-302 IR spectrophotometer. The ^{1}H-NMR spectra were recorded on Bruker-FT- WP-100SY instruments using tetramethylsilane as internal standard.

N-Benzyl-3-indole acetic acid (2)

NaH (4.8g, 0.2 mole) was stirred in dry THF for 10 minutes. 3-Indole acetic acid (1.4 gm, 0.008 mole) was added and the solution stirred for 45 minutes. Benzyl chloride (4.8 ml, 0.040 mole) in THF (40 ml) was added dropwise (10 minutes) and the solution refluxed for 12 hours. The product was cooled and diluted with water (150 ml), acidified with dil. HCl, extracted with EtOAc and dried over

anhydrous Na_2SO_4. After removal of the solvent it was chromatographed on silica gel using pet. ether: ethylacetate (60:40). A pale yellow band was eluted out, which on evaporation gave N-benzyl-3-indole acetic acid, (T.L.C., 8% CH_3OH in chloroform, Rf values 0.212), 1.36g (80%).

MS (m/z): 265($C_{17}H_{15}NO_2$, 20%), 220 (24%), 130 (100%), 91 (54%).
IR ($CHCl_3$): 1710 cm^{-1}.
UV (MeOH): λ_{max} 209, 261, 297 λ_{min} 255, 265 and 283 nm.
^{1}H-NMR ($CDCl_3$): δ3.83 (s, 5H), δ 5.29 (s, 2H), δ 6.9-7.6 (m, 4H, Ar-H).

N-Benzyl-3-indole methyl acetate (3)

N-Benzyl-3-indole acetic acid (1.36g, 0.005 mole) was dissolved in anhydrous methyl alcohol (130 ml) and sulphuric acid (3 drops) was added; the solution was stirred for 24 hours at 25°C. This was then evaporated to give a gum. The gum was dissolved in ethyl acetate (100 ml) and washed twice with 10% sodium carbonate solution (2 x 150 ml) and then washed with water (2 x 100 ml). The ethyl acetate layer was dried with sodium sulphate and evaporated under vacuum. The reddish coloured oily product was chromatographed using ethylacetate: pet. ether (20:80) on silica gel. A pale yellow fast moving band developed which on elution and evaporation gave the pure ester, 1.13 g (80%).

MS (m/z): 279 ($C_{18}H_{18}NO_2$, 21.5%), 220 (50%), 130 (48.2%), 91 (100%).
IR ($CHCl_3$): 1715 cm^{-1}
UV (MeOH): λ_{max} 275, 285, 297 λ_{min} 278, 294 nm.
^{1}H-NMR ($CDCl_3$): δ 2.95 (t, 2H), δ 3.83 (s, 5H), δ5.27 (s, 2H), δ 7.1-7.55 (m, 4H, Ar-H).

N-Benzyl-3 β-(hydroxy-ethyl) indole (4)

The ester (3) (1.13g, 0.0041 mole) was dissolved in anhydrous ether (50 ml), and fresh lithium aluminium hydride (0.5 g) was added. The solution was stirred at room temperature for one hour, during which the pale yellowish green colouration disappeared.This was then further stirred overnight at room temperature. Excess of LAH was destroyed by carefully adding drops of water with stirring. Ethyl acetate (50 ml) was added and the salts of aluminium and lithium were filtered off. The organic layer was separated, washed once with water and then dried over anhydrous sodium sulphate. The dried product was filtered off and concentrated. The residue was chromatographed by using chloroform as the eluent. The light yellow slow-moving band was collected, which on evaporation gave the pure alcohol (0.6 g, 60%).

MS (m/z): 251 ($C_{15}H_{17}NO$ 22%), 220 (50%), 91(100%)
IR ($CHCl_3$): 2800 cm^{-1}
UV (MeOH): λ_{max} 208, 223, 286 λ_{min} 215, 250 nm.
^{1}H-NMR ($CDCl_3$): δ 2.95 (t, 2H), δ 3.83 (s, 5H), δ5.27 (s, 2H), δ 6.9-7.55 (m, 4H, Ar-H).

N-Benzyl-3-β (-bromo-ethyl)-indole (5)

In a two-necked flask fitted with a condensor and a magnetic stirring device, the alcohol (4) (0.6 gm, 0.003 mole) was dissolved at room temperature in anhydrous benzene (15 ml) and to this magnetically stirred mixture, phosphorous tribromide (0.40 ml, 0.0046 mole) was added at room temperature. After addition, a dark orange colouration was formed.This was then stirred and refluxed for three hours during which time the colour changed from orange to yellow. After cooling, 10% aqueous sodium carbonate solution was added. This was extracted twice with ethyl acetate. The ethyl acetate layer was washed twice with water and dried over anyhydrous sodium sulphate. After removal of solvent the product was chromatographed on silica gel using pet. ether: ethyl acetate (80:20) mixture. The cream-coloured fast moving band was collected, which on concentration gave the pure N-benzyl-bromo ethyl indole (0.45 g, 64%).

MS (m/z): 315/313 ($C_{17}H_{16}NBr$, 8%), 220 (38%), 167 (55%), 149 (100%) 94 (60%) 91 (54%).
IR ($CHCl_3$): 1630, 1360, 1175 cm^{-1}
UV (MeOH): λ_{max} 221, 275, 286 λ_{min} 256, 280 nm.
^{1}H-NMR ($CDCl_3$): δ 3.83 (s, 5H), δ 5.27 (s, 2H), δ6.9-7.5 (m, 4H, ArH).

N-Benzyl-3 β-(3-ethylpyridinium bromide) ethyl indole (6)

N-Benzyl tryptophyl bromide (0.45 g, 0.00143) was dissolved in dry ethyl acetate (4 ml) and then placed in a sealed tube, 3-ethyl pyridine (0.03 ml) in 1 ml dry ethylacetate was added to it, and the solution heated in the sealed tube at 120°C for 72 hours.

On cooling, the tube was opened. A thick viscous brownish fluid separated out which was initially washed with a little dry ethyl acetate and then with pet. ether. The above thick viscous fluid was then dissolved in ethyl acetate containing 8% anhydrous methanol, and the solvents were then removed on a rotary evaporator. This gave a yellowish brown solid, which on tlc using either 91% chloroform in 9% methanol or dichloromethane: ethylacetate: methanol (70:20:10) gave a single spot (0.36 gm, 73%).

MS (m/z): 342 ($C_{24}H_{26}N_2$, 2%), 234 (145), 220 (46%), 107 (22%) 91 (100%).
IR ($CHCl_3$): 3120, 3000, 1630, 1619 cm^{-1}
UV (MeOH): λ_{max} 202, 220, 268 λ_{min} 210, 249 nm.
^{1}H-NMR ($CDCl_3$): δ 1.04 (t, 3H), δ 2.02 (q, 2H), δ5.27 (s, 2H), δ 7.2-7.8 (m, 4H, Ar-H).

N-Benzyl-3-β-(1,2,5,6 ethyl tetrahydropyridyl) ethylindole (7)

The pyridinium salt (6) (0.036 gm, 0.001 mole) was dissolved in anhydrous methanol (30 ml) and to this triethylamine (0.5 ml) was added. The mixture was stirred at 0°C for half an hour. Sodium borohydride (0.3 gm) was then added in small portions and the solution further stirred at 0°C for 1 hour. A yellowish brown colour developed during this reaction. The solvent was removed under vacuum, and by addition of 10% hydrochloric acid (5 ml) at 0°C with stirring, the pH was brought to pH 1.5. This gave a sticky reddish brown gum. The mixture was further stirred for 10 minutes and the temperature was brought at 25°C. A saturated solution of sodium carbonate was then added slowly and the reaction mixture was made slightly alkaline, and extracted with CH_2Cl_2. The dichloromethane extract was washed with water, dried over anhydrous sodium sulphate, filtered and evaporated under vacuum to give a reddish brown gum, tlc with 91% chloroform in 9% methanol showed that about 90% conversion had been taken place. The material was subjected to column chromatography on silica gel using ethyl acetate: chloroform (20:80) mixture. A colourless band was collected and the solvents evaporated under vacuum. The product appeared to be slightly impure and was hence rechromatographed on silica gel using acetone: pet. ether (3:7), which gave the pure product (0.24 g, 70%).

MS (m/z): 344 ($C_{24}H_{28}N_2$, 10%), 220 (20%), 124 (100%), 91 (25%).
IR ($CHCl_3$): 1600 cm^{-1} (C=CH)
UV (MeOH): λ_{max} 206, 222, 288, λ_{min} 213, 240 nm.
^{1}H-NMR ($CDCl_3$): δ 1.04 (t, 3H), δ 2.02 (q, 2H), δ5.45 (s, 1H), δ 7-7.8 (m, 4H, Ar-H).

N-Benzyl-2-pyruvoyl-3 β (1,2,5,6-tetrahydropyridyl)-ethyl indole (8)

Aluminium chloride was dried under high vacuum for four hours before use. The above predried aluminium chloride (0.2 gm) and dichloromethane (5 ml dried over $CaCl_2$) were placed in a three-necked flask which was magnetically stirred. A nitrogen gas inlet, a condensor with moisture proofing top and a rubber septum were connected to the flask. The mixture was gently stirred for five minutes. Methylmono-oxalyl chloride (1.4 ml) was added with the help of a syringe. The solution was stirred gently under nitrogen atmosphere at room temperature for thirty minutes. The tetrahydro derivative (0.1 gm) dissolved in dichloromethane (0.5 ml) was added with the help of a syringe, under nitrogen atmosphere. The mixture was then stirred very gently and the temperature maintained at 40°C for 5-1/2 hours. After the reaction, the contents of the flask were poured into ice-cold 15% HCl (35 ml). Dichloromethane (25 ml) was added and the organic layer separated out. This was washed twice with water (50 ml), then with 10% Na_2CO_3 solution (30 ml), again thrice with water (100 ml) and dried overnight over anhydrous Na_2SO_4. The solution was filtered and concentrated on a rotary evaporator. The residue was passed through a column of silica gel. Elution was done using pet. ether: acetone (70:30) and ten fractions (5-6 ml) were collected. A pale yellowish band came off the column (leaving a dark yellow band at the top) which gave a single spot of the required product on tlc (pet. ether: acetone 60:40) (8) 0.06 g, (60%).

MS (m/z): 430 ($C_{27}H_{30}N_2O_3$, 10%), 319 (5%), 260 (8%), 124 (100%) 91 (90%).
IR ($CHCl_3$): 1735, 1640 cm^{-1}
UV (MeOH): λ_{max} 206, 323, λ_{min} 270 nm.
^{1}H-NMR ($CDCl_3$): δ 1.02 (t, 3H), δ 2.09 (q, 2H), δ3.95 (s, 3H), δ 5.49 (m, 1H) 7-7.8 (m, 4H, Ar-H).

N-Benzyl-3 β (3-chloro-1,2,5,6-Tetrahydropyridyl-ethyl) indole

When the Friedal Craft's acylation was carried out by using the tetrahydro derivative (0.1 g) with the stock anhydrous aluminium chloride without predrying under the above experimental conditions, a chloro-derivative was formed instead of the required acylated product (0.50g, 45%).

MS (m/z): 382 (4%) and 380 ($C_{24}H_{29}N_2Cl$, 1.5%), 344 (2%), 220 (10%), 160 (100%) 124 (26%), 91 (65%).

N-Benzyl-2-pyruvoyl-3 β (1,2,5,6-3-ethyl tetrahydropyridyl ethyl) 2 indolyl acrylate. (9)

In a two necked flash and under nitrogen atmosphere, methyl triphenyl phosphonium bromide (0.3 g) was placed in sodium dried ether (15 ml) and then 5% solution of methyl lithium (0.3 ml) was added. The solution was stirred at room temperature for two and a half hours. The pyruvate (0.018 gm) in dried ether (0.5 ml) was then added and the solution further stirred for ten minutes and then kept at -20°C. After 96 hours, CH_2Cl_2 (5 ml) and water (2 ml) were added. The aq. layer was separated out and the organic layer was once again washed out with water. The organic layer was evaporated, anhydrous ether was added and the ether- soluble part was separated from the undissolved part. The solvent was removed, tlc was carried out in pet. ether: dichloromethane: methanol (5:3.2). On staining with iodine, a spot was observed which had a different Rf value then the starting material. The product N-benzyl secodine was obtained by preparative tlc (yield, 15%).

MS (m/z): 428 ($C_{28}H_{32}N_2O_2$, 6%), 304 (5%), 293 (6%), 215 (100%), 201 (100%), 124 (30%), 91 (20%).
IR ($CHCl_3$): 1730 cm^{-1}
UV (MeOH): λ_{max} 220, 259, 275, 295 λ_{min} 250, 260 nm.

^{1}H-NMR ($CDCl_3$): δ 1.02 (t, 3H), δ 2.09 (q, 2H), δ3.81 (s, 3H), δ 5.15 (m, 1H), δ 6.45 (d, 1H, H_b-17), δ6.9 (d, 1H, H_a-17), δ 7-7.8 (m, 4H, Ar-H).

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