

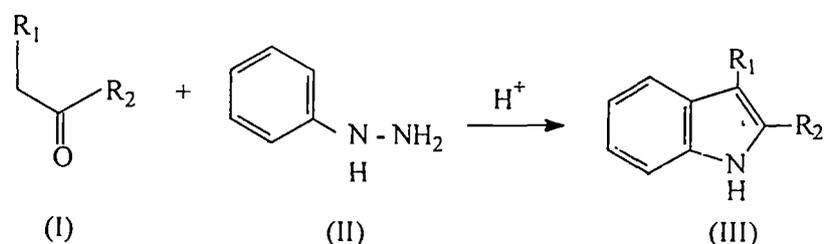
Chapter Two

Steroidal Indole

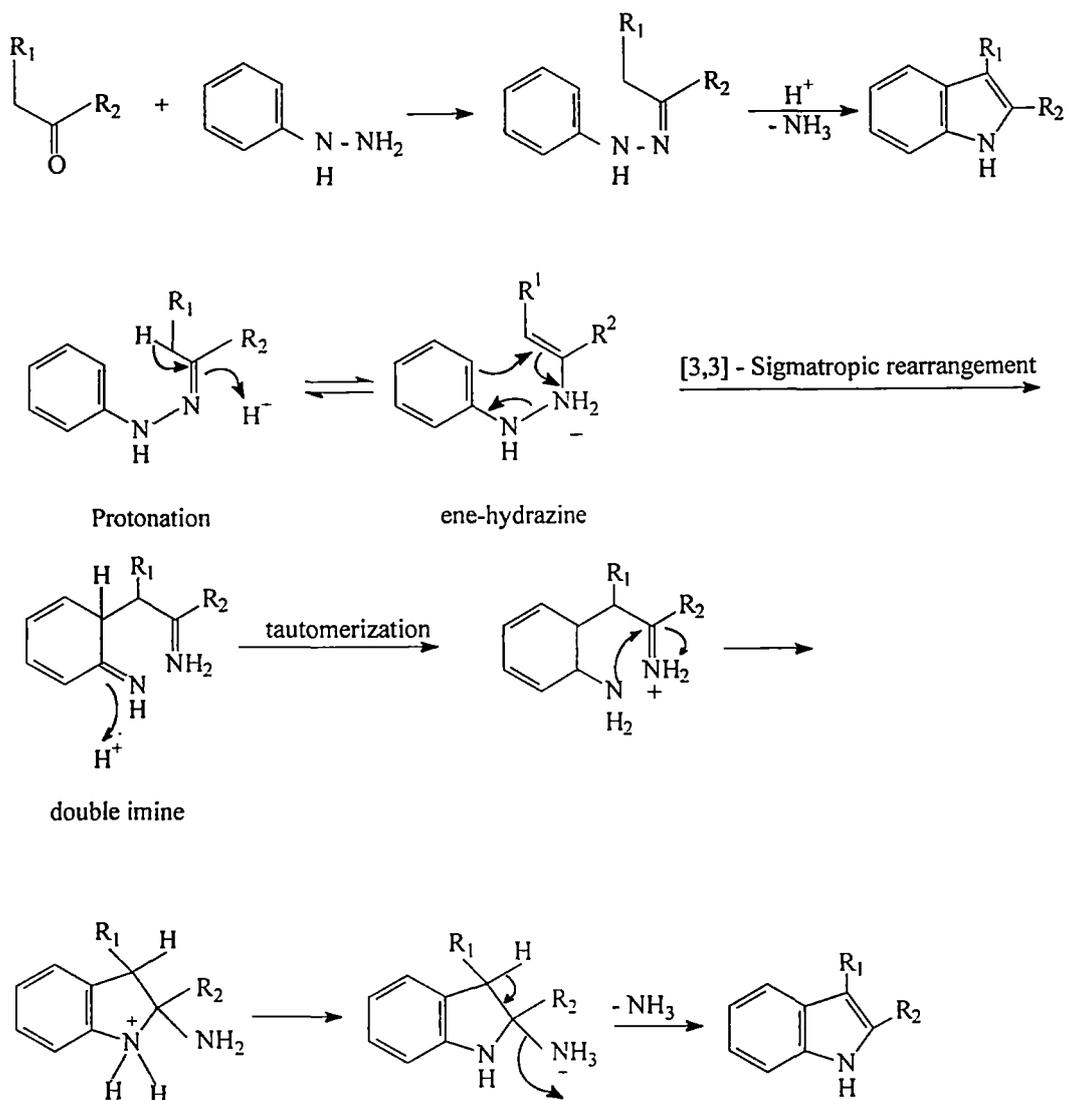
Theoretical

Indoles are aromatic heterocyclic organic compounds having a bicyclic structure, consisting of six membered benzene ring fused to a five membered nitrogen-containing ring. Participation of the nitrogen lone pair in the aromatic ring means that indole is not a base and it does not behave like a simple amine. Indoles are a large family of natural and synthetic compounds with wide ranging biological activities the biological activities of indole has been reviewed of Baeyers¹. Indoles may be used in the manufacture of pharmaceutical intermediate in alkaloids synthesis. The first reported indole ring synthesis has given by Emil Fischer² in 1883 by the condensation of ketone with phenylhydrazine in presence of lewis acid. Indole and its derivative continue to capture the attention of synthetic chemists and as a result large number of original indole ring synthesis have been reported. Warnhoff *et al.*³ and Ban *et al.*⁴ have reported the synthesis of steroidal indoles in the recent past. Robinson⁵ has given a good account of indoles and mechanism of their formations.

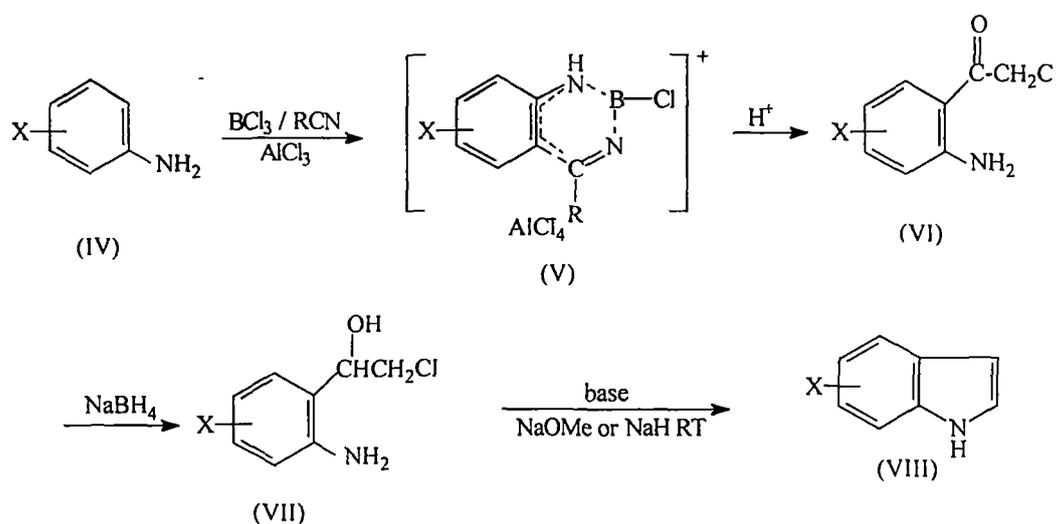
This chapter deals with some important and recent studies regarding the indole synthesis. Fischer *et al.*⁶ have reported the indole synthesis in 1883 by the condensation of ketone (I) with phenylhydrazine (II) in the presence of Lewis acid afforded indole (III) as a resultant product.



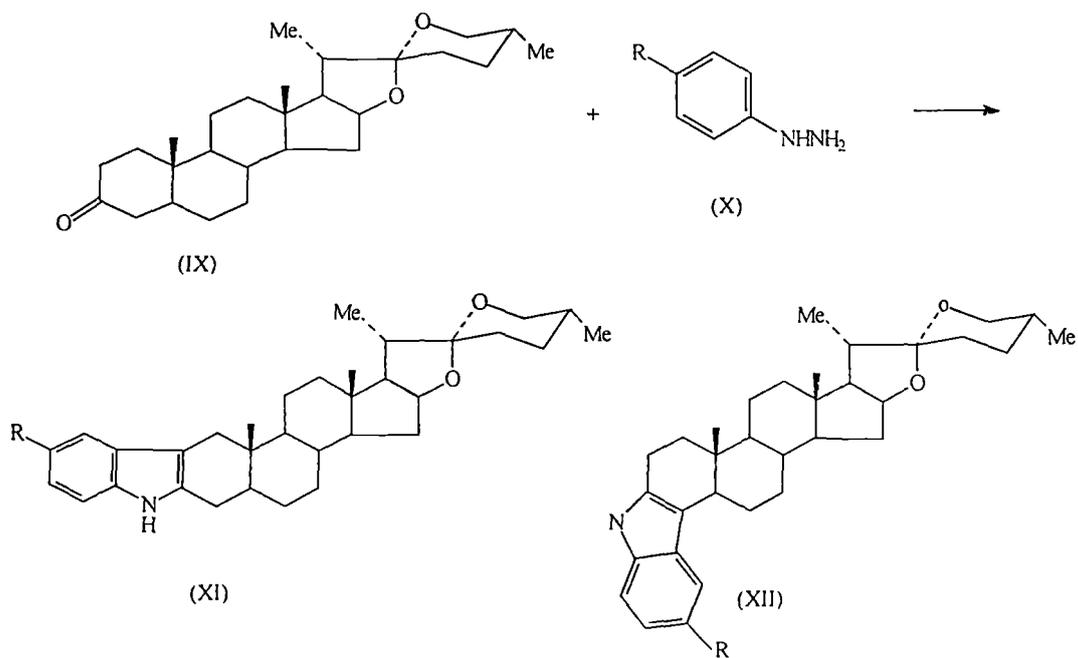
Mechanisms:



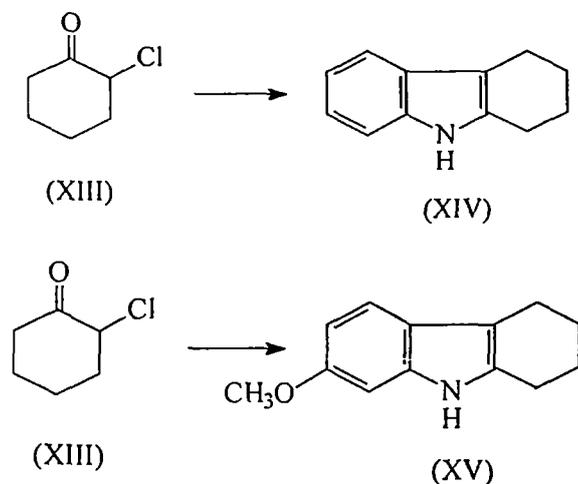
Sugasawa *et al.*⁷ have reported the synthesis of indole and the preparation involved specific orthochloroacetylation of aniline to give 2-amino- α -chloroacetophenone (V) followed by reductive cyclization of (V) with sodiumborohydride in refluxing dioxin giving intermediate α -chloromethylbenzyl alcohol (VI) which gives indole (VII) under basic condition.



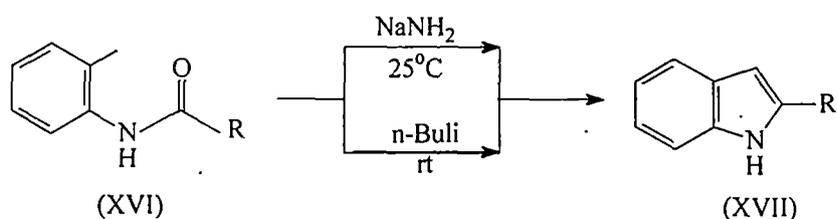
The Fisher indole synthesis of 5 α -spirostan-3-one (IX) with 4-R C₆H₄NHNH₂ gave indolospirostenes (X) whereas 5 β -spirostan-3-one gave the isomeric indolospirostenes (XI)⁸.



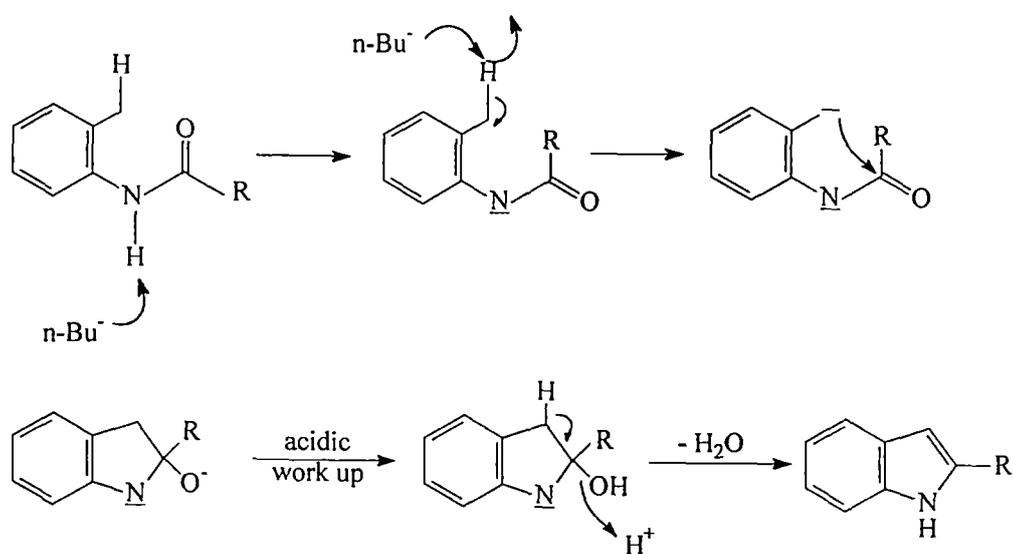
Paul A. Wender⁹ and Alan W. White, have reported an efficient synthesis of indole derivative in one operation by reaction of organolithium reagents with vicinal dication equivalent.



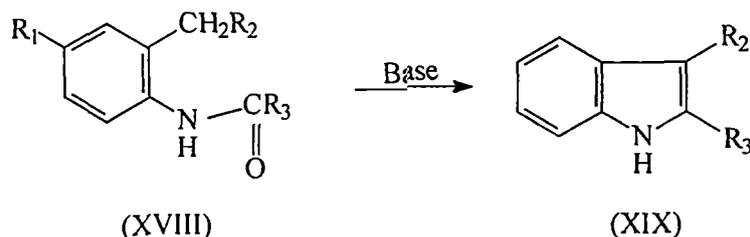
Madelung¹⁰ have reported the preparation of Indoles from the intramolecular cyclization of 2-(acylamino)- toluenes using strong bases.



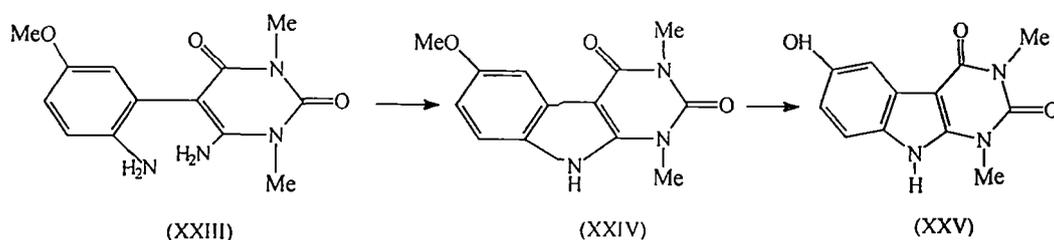
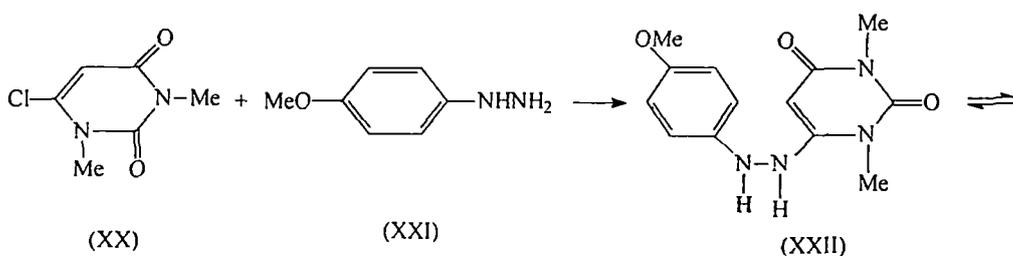
Mechanism:



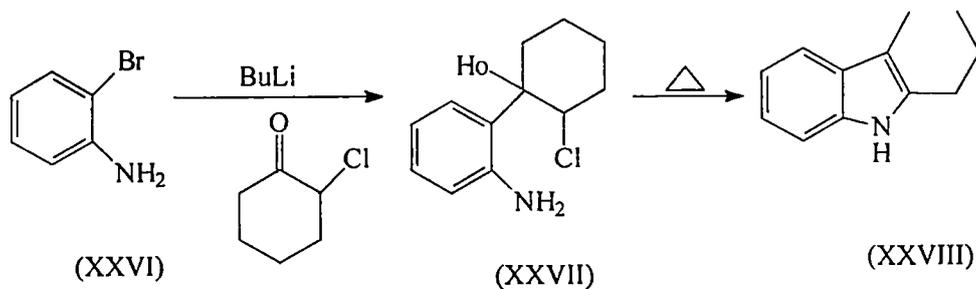
Houlihan *et al.*¹¹ have reported a modified Madelung version of indole synthesis, involving the intramolecular cyclization of an N-(2-alkylphenyl) alkanamide (XVIII) by a strong base at elevated temperature to afford indole (XIX).



Bernier *et al.*¹² have reported the preparation of 6-hydroxypyrimido[4,5-b] indole (XXV) ring which involves the reaction of 1,3-dimethyl-6-chlorouracil (XX) with p-methoxyphenylhydrazine (XXI) in presence of sodium carbonate. The diamine (XXIII) obtained undergo cyclization to give 9H-pyrimido [4,5-b] indole (XXIV) on refluxing either in 98% formic acid or dimethyl aniline which on heating at 200°C with pyridiniumchloride afforded 6-hydroxy pyrimido [4,5-b] indole as a resultant product (XXV).

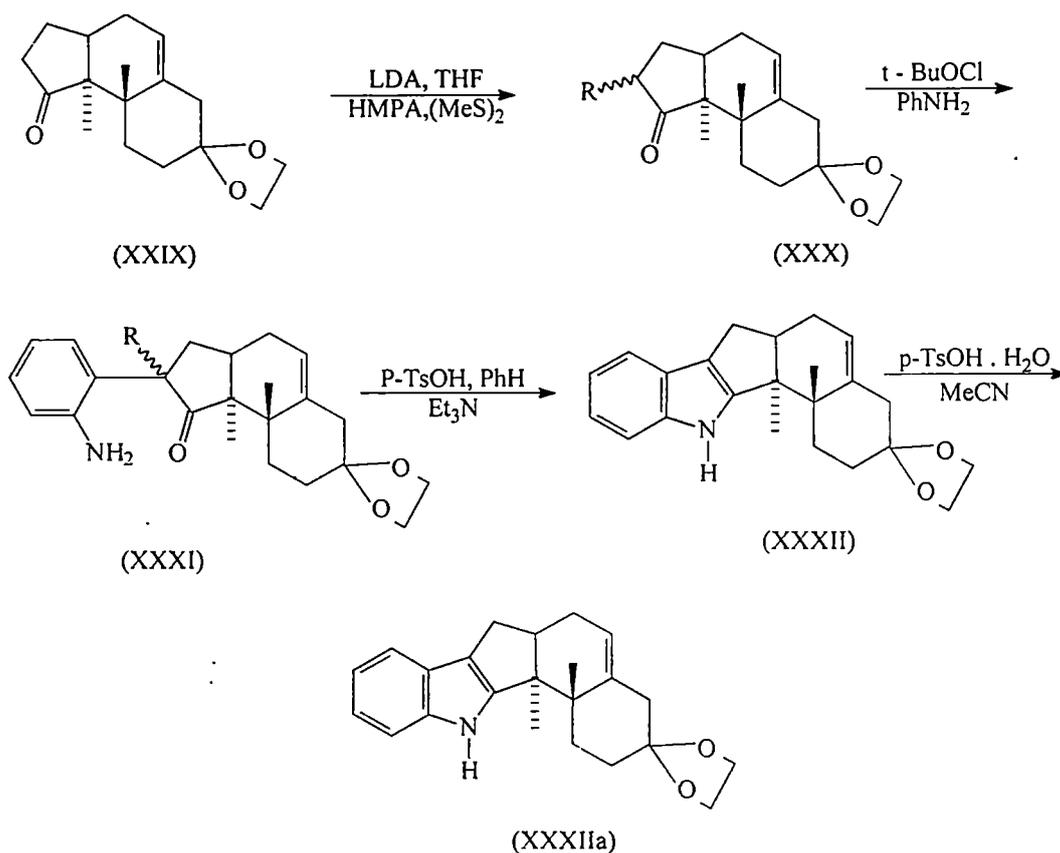


Wender *et al.*¹³ have reported the synthesis of indole (XXVIII) by treatment of 2-bromoaniline (XXVI) with t-butyllithium (3equiv) and 2-chlorocyclohexanone, which afforded amino alcohol (XXVII) as an intermediate. Heating (XXVII) with pyrimidine in DMF gave the indole.



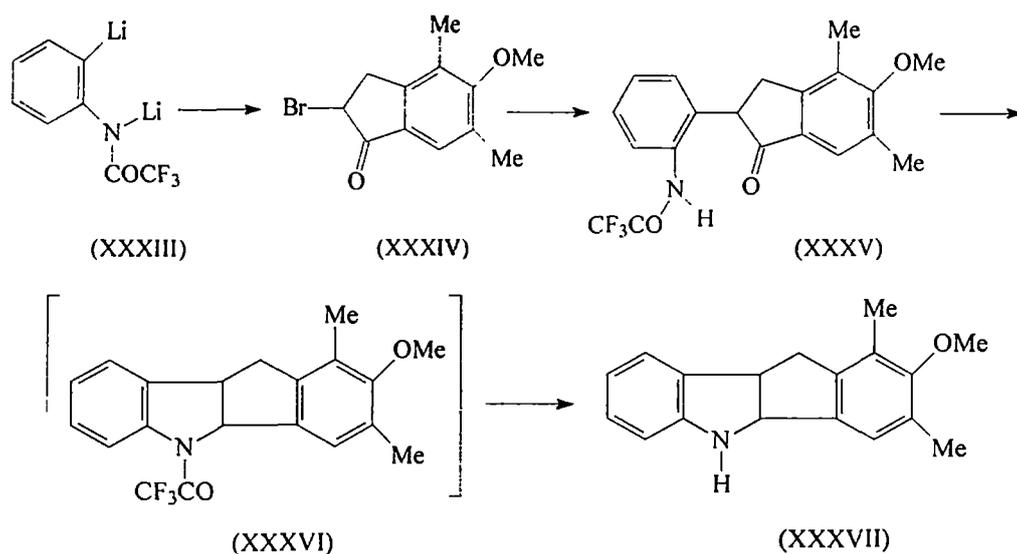
Smith *et al.*¹⁴ have given the synthesis of indole ketal (XXXII) according to the following scheme-I

SCHEME - I

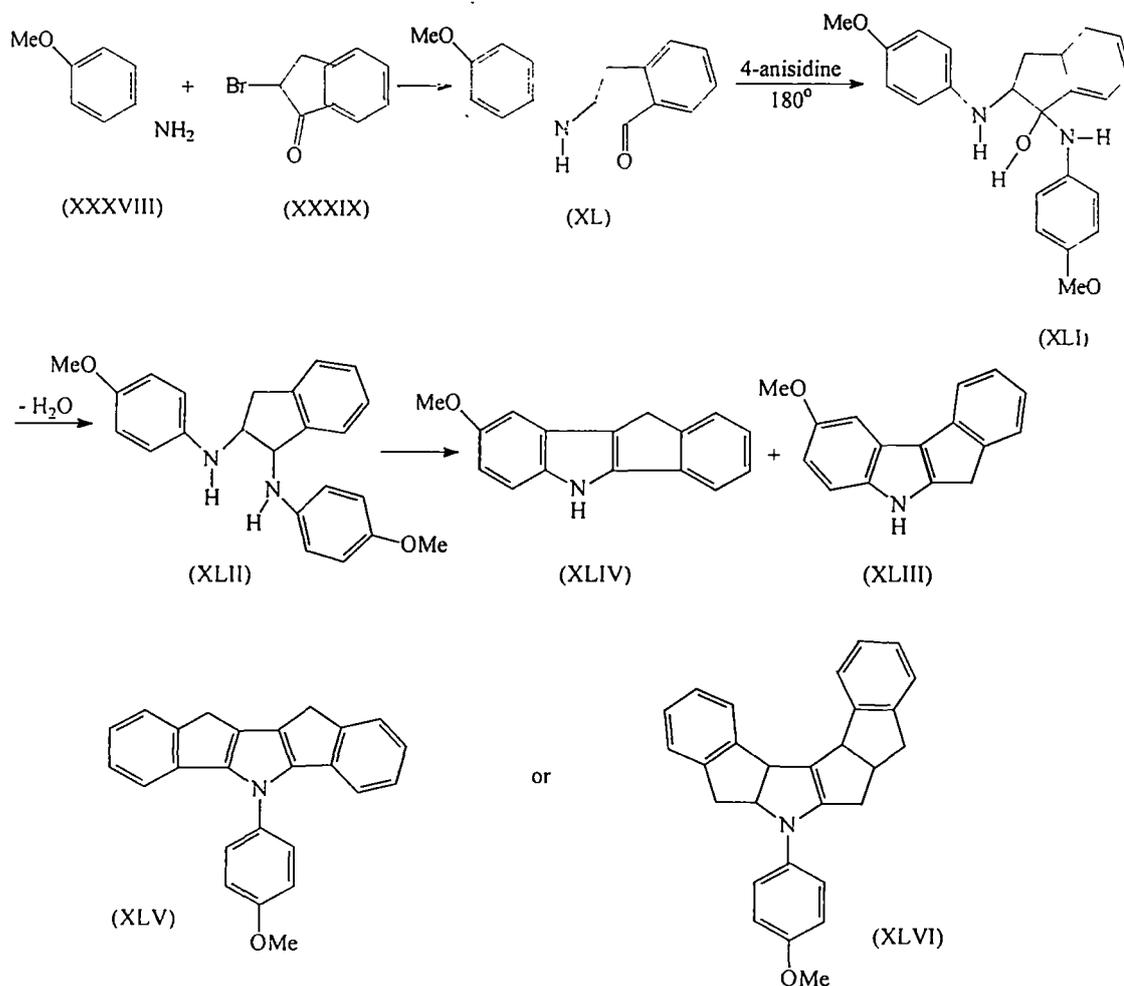


R = SMe / H

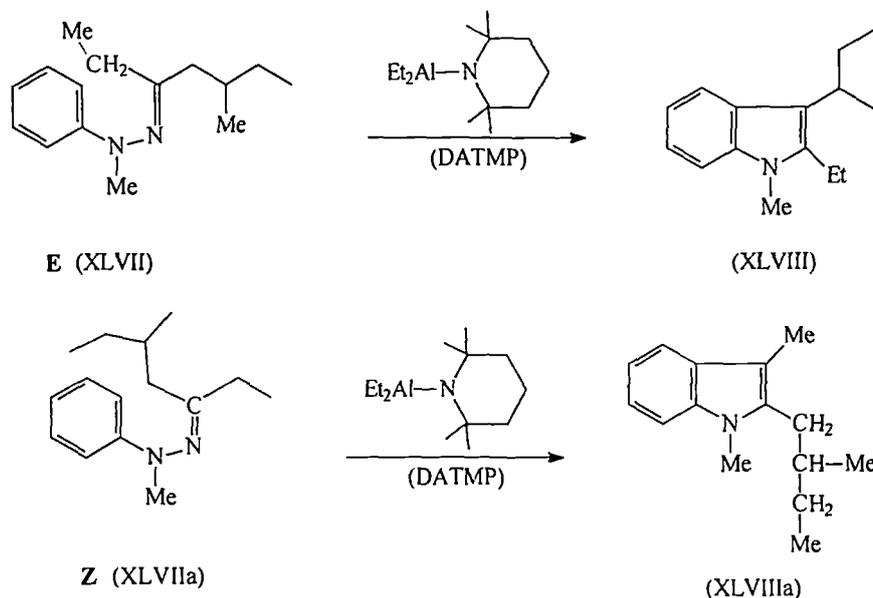
The Wender and Bischler indole synthesis have been investigated as potential routes to dihydroindenoindole. Thus a Wender reaction between N,2-dilithio-N-trifluoroacetylaniline (XXXIII) and 2-bromo-5-methoxy-4,6-dimethyl-indanone (XXXIV) affords the corresponding dihydroindeno [1,2-b] indole¹⁵ (XXXVII).



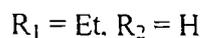
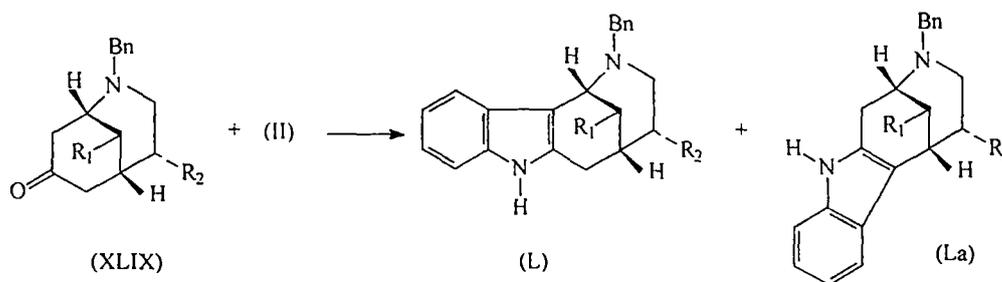
Same authors¹⁵ also report that, in a Bischler reaction between 4-methoxyaniline (XXXVIII) and 2-bromoindanone (XXXIX) both 8-methoxydihydroindeno [1,2-b] indole (XLIII) and 9-methoxydihydroindeno [2,1-b] indole (XLIV) were formed in low yields along with other products (XLV, XLVI).



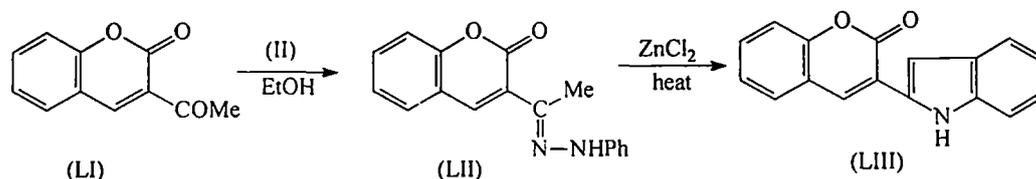
Maruoka *et al.*¹⁶ have reported regioselective Fischer Indole synthesis mediated by organoaluminum amide. In this preparation, diethyl aluminium 2,2,6,6-tetramethylpiperidine (DATMP) reacted with (E)-N-methyl-N-phenylhydrazone of 5-methyl-3-heptanone (XLVII) to give 3-sec-butyl-2-ethyl-1-methylindole (XLVIII) as the sole product. The Z isomer (XLVIIa) affords 1,3-dimethyl-2-(2-methyl butyl) indole (XLVIIIa) with high regioselectivity under similar reaction conditions.



Gracia *et al.*¹⁷ have reported the synthesis of (1RS, 5RS, 12SR) 2- Benzyl -12-ethyl-1,2,3,4,5,6-hexahydro-1.5-methanoazocino[4,3-b]indole (L) by the treatment of 2-azabicyclo[3.3.1]nonane-7-one (XLIX) with phenylhydrazine (II).

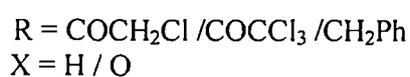
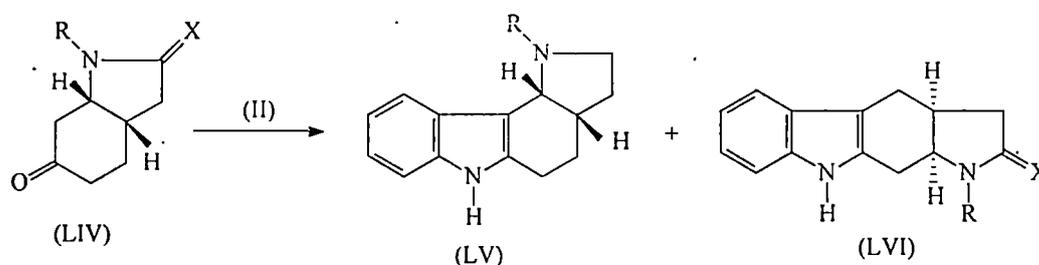


Laxmi Rao and Arya K. Mukerjee¹⁸ have reported the synthesis of indoles by the condensation of 3-acetylcoumarin (LI) with phenylhydrazine (II) in ethanol gave phenylhydrazone (LII). Further phenylhydrazone(LII) forms 3-(indol-2-yl)coumarin on heating with anhyd. zinc chloride.

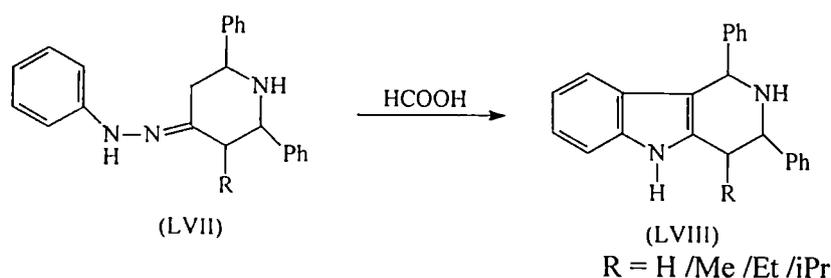


Bonjoch *et al.*¹⁹ have reported the preparations of cis-1-(chloroacetyl)-1,2,3,3a,4,9,10,10a-octahydropyrolo [2,3-b]carbazole (LV) and cis-1-(tri-chloroacetyl)-1,2,3,3a,4,9,10,10a-octahydropyrolo[2,3-b]carbazole (LVI), shown by the following scheme.

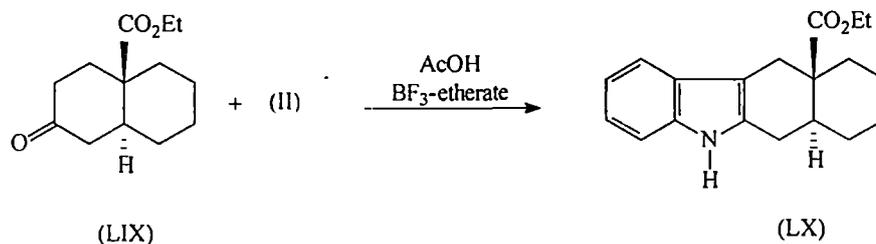
SCHEME – II



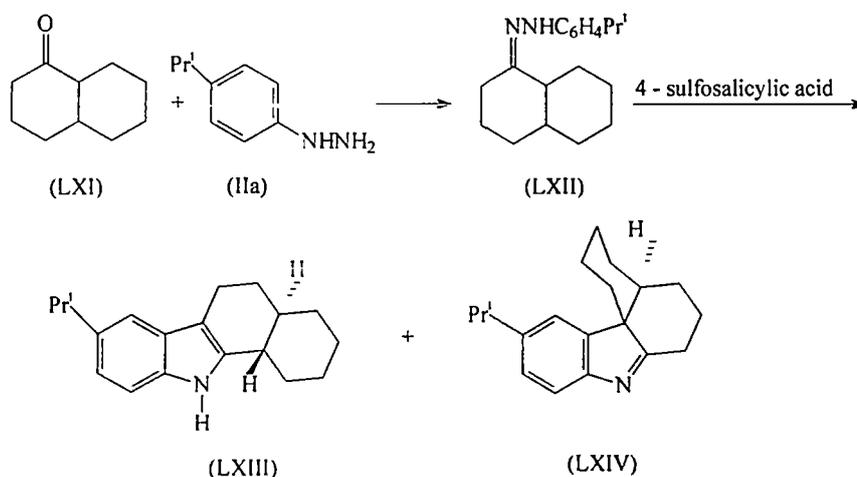
Murugesan *et al.*²⁰ have synthesized corresponding diphenyl-1,2,3,4-tetrahydro- γ -carbolines(LVIII) from the phenylhydrazone derivative of 2,6-diphenyl piperdin-4-one (LVII) by using formic acid as a solvent as well cyclizing agent.



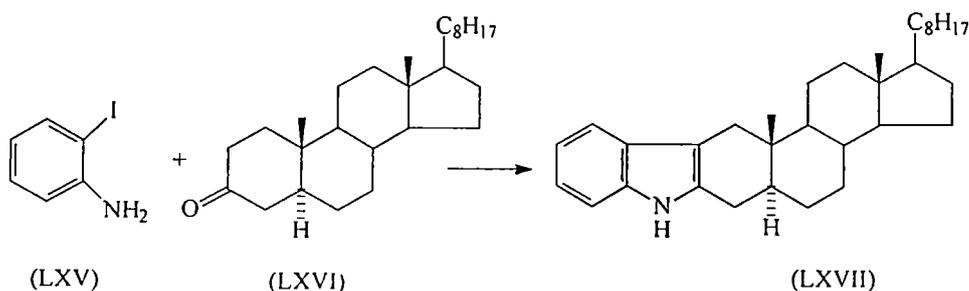
Atarashi *et al.*²¹ have reported that by the treatment of ketone (LIX) with phenylhydrazine (II) and borontrifluoride etherate in acetic acid gave the expected indole (LX).



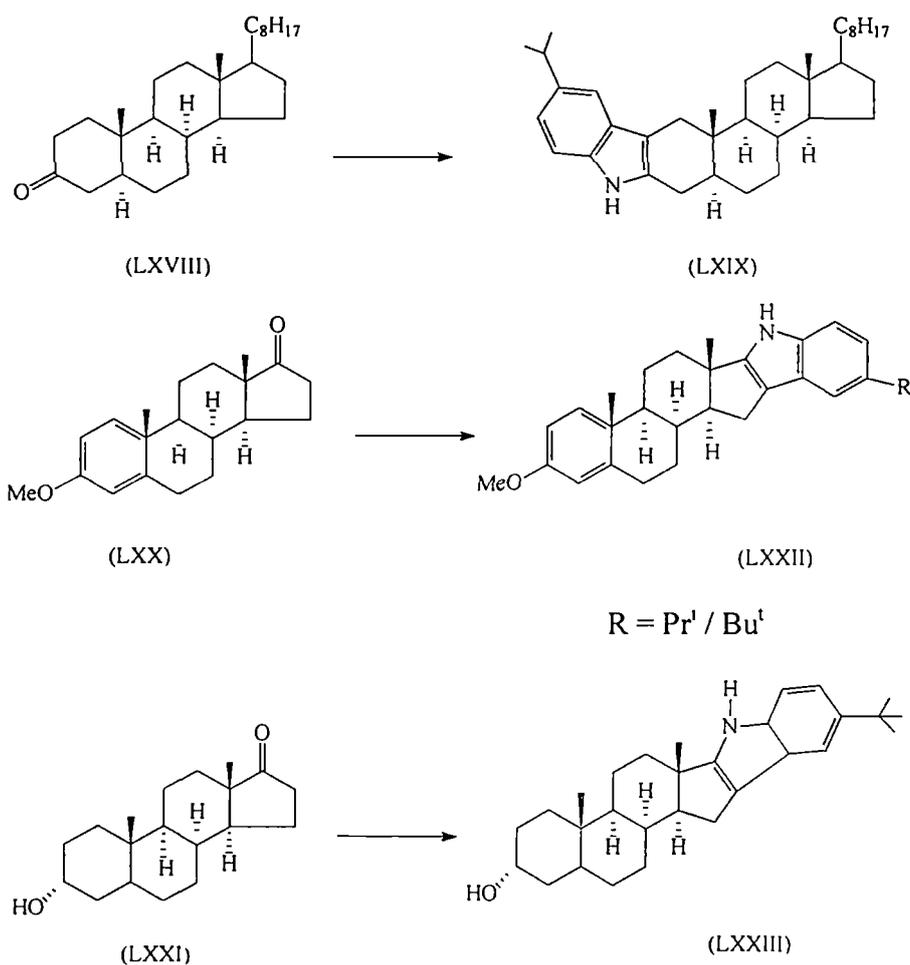
Brown *et al.*²² synthesized 2,3,4,4a,5,6,11,11b-octahydro-8-isopropyl-1H-benzo[a]-carbazole (R=Pr¹) (LXIII) and 1,2,3,4,4a,5,6,7-octahydro-11-isopropylbenzo[d]-carbazole (LXIV) by the treatment of 1-decalone (LXI) with 4-isopropylphenylhydrazine (IIa) mixture of hydrazone (LXII) is formed which in the presence of 4-sulfosalicylic acid cyclise to yield main product indole (LXIII) and indolenine (LXIV).



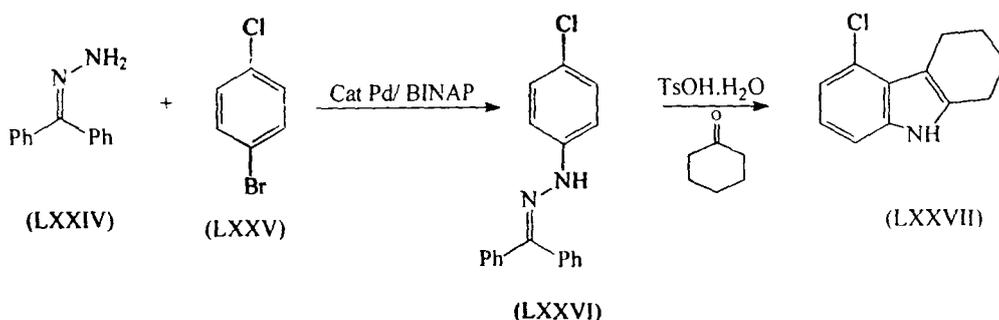
Cheng-yi Chen *et al.*²³ have reported a new and efficient method for indole synthesis (LXVII) using a palladium catalyzed annulation between o-iodoaniline (LXV) with 5 α -cholestan-3-one (LXVI) affording the indolo cholestan (LXVII).



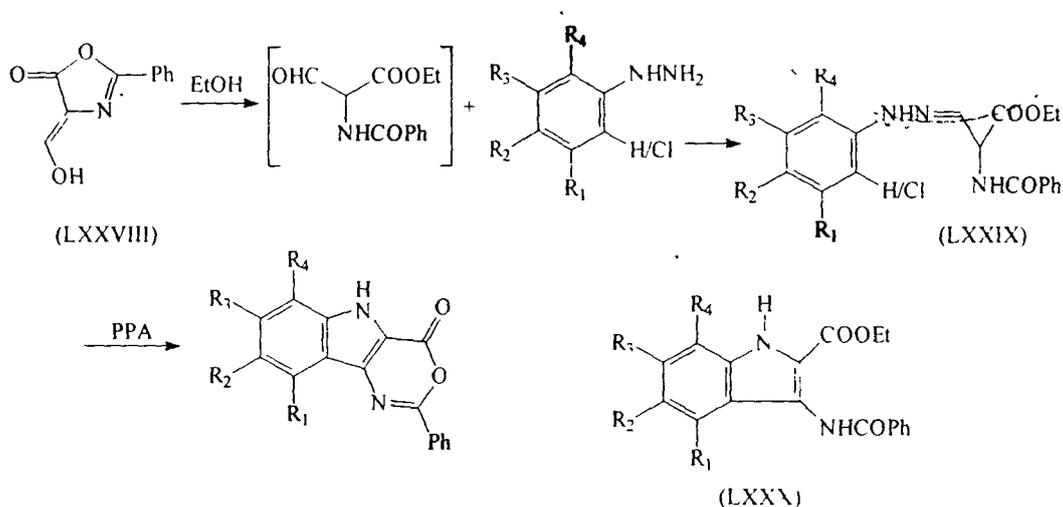
Brown *et al.*²⁴ have given the synthesis of some novel 10-Isopropyl-7H-5 α -cholestanone [3,2-b]indole (LXIX). Condensation reaction between 5 α -cholestan-3-one (LXVIII) with 4-isopropylphenylhydrazide hydrochloride gave the hydrazone which on indolisation in glacial acetic acid using 4-sulfosalicylic acid gave a single indole (LXIX). Further O-methylestrone (LXX) and 3 α -hydroxy-5-androstr-17-one (LXXI) gave indoles (LXXII) and (LXXIII) respectively. These compounds have been observed to act as chain-breaking antioxidant²⁴.



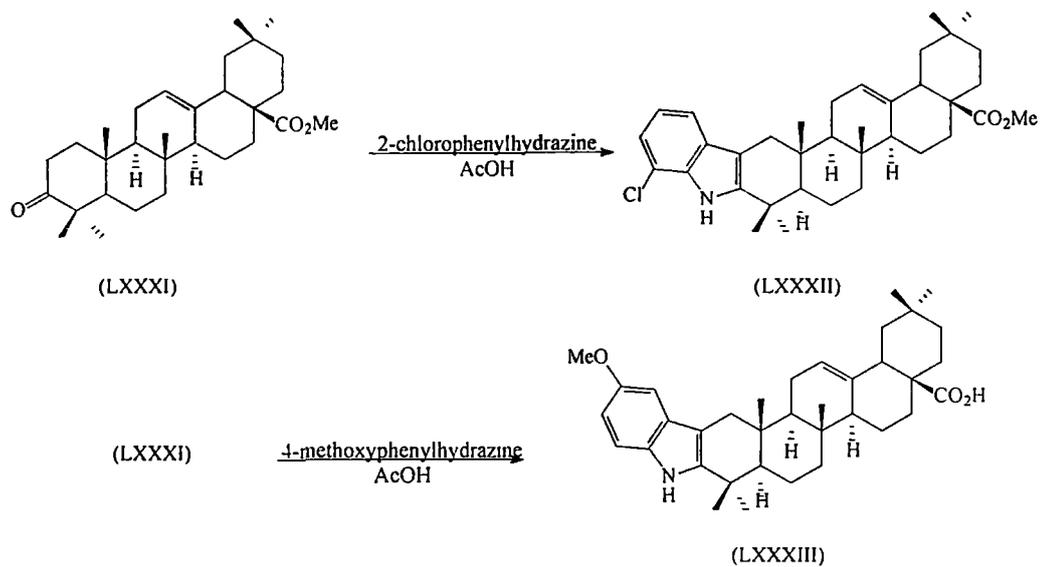
Wagaw *et al.*²⁵⁻²⁶ have reported the synthesis of indole by the treatment of hydrazone (LXXIV) with aryl bromide (LXXV) in presence of palladium as catalyst. The N-arylhydrazone (LXXVI) obtained on subsequent reaction with ketone under acidic conditions afforded resultant product (LXXVII).



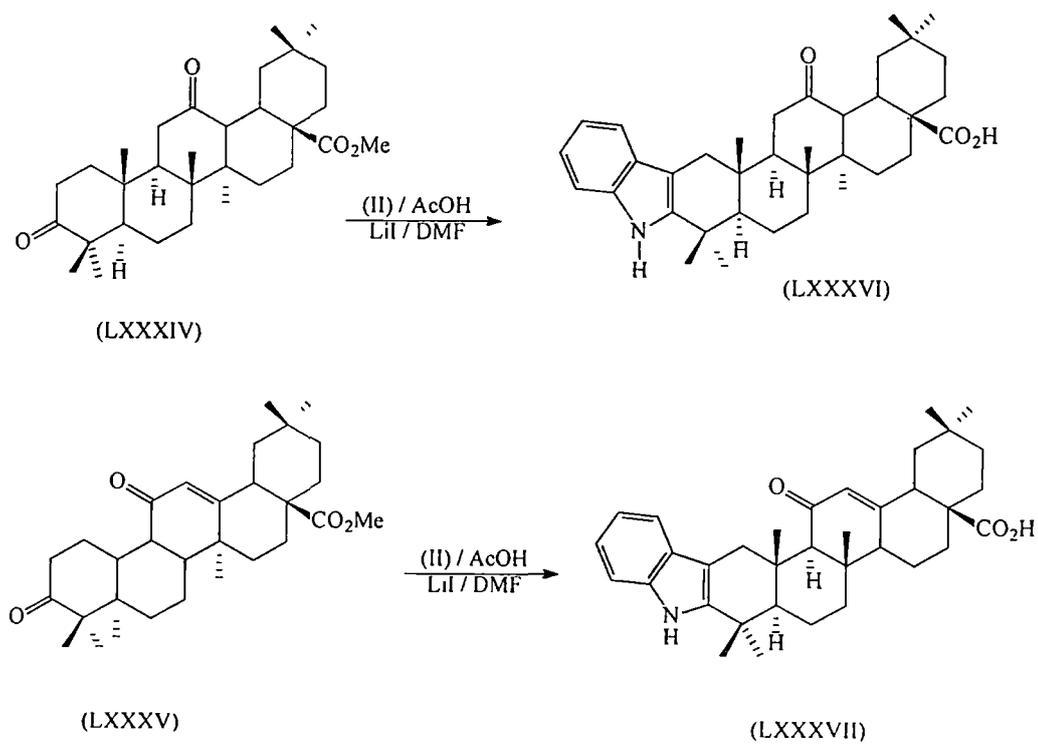
Ethyl 2-benzoylamino-3-(phenylhydrazone) propanoate derivatives (LXXIX) prepared from 4-hydroxymethylene-2-phenyl-5-(4H)-oxazolone (LXXVIII) and phenylhydrazine (II) in ethanol was converted to ethyl-3-(benzoylamino)-1H-indole-2-carboxylates (LXXX) by heating with polyphosphoric acid followed by sodium ethoxide.²⁷

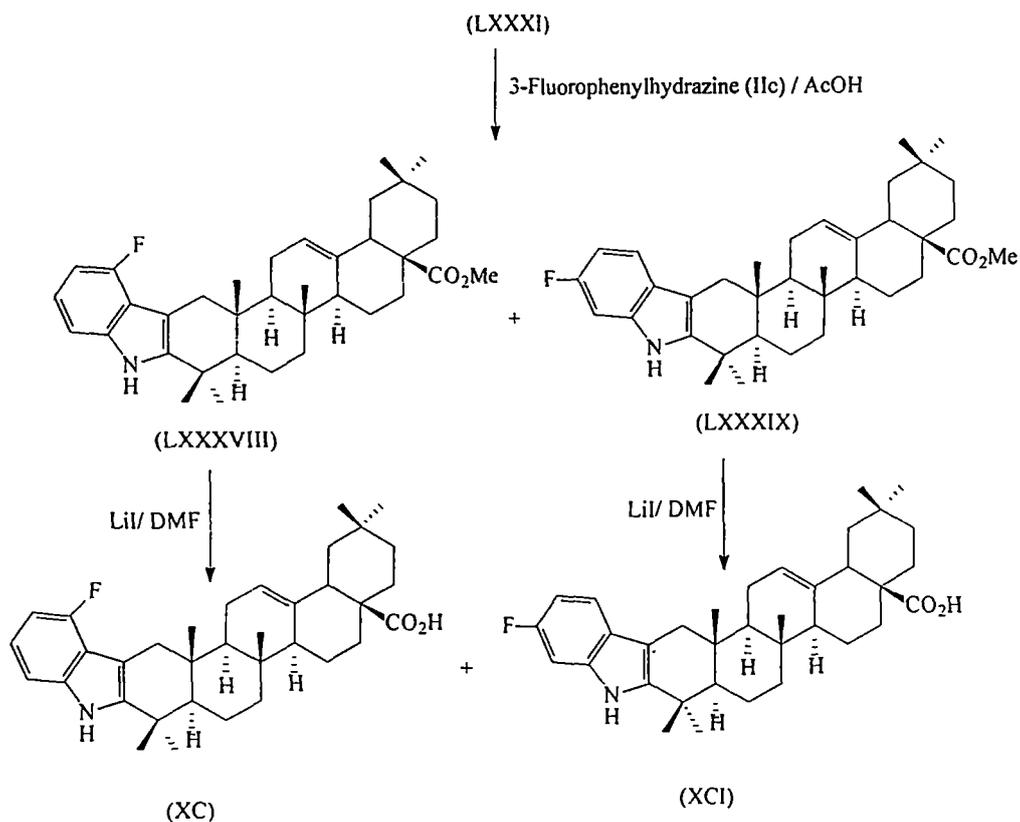


Gribble *et al.*²⁸ have reported the synthesis of steroidal indole by the treatment of the reaction between ketone ester (LXXXI) with 2-chlorophenylhydrazine and 4-methoxyphenylhydrazine in acetic acid giving the fused indole ester (LXXXII) and (LXXXIII) respectively in 90% yield.

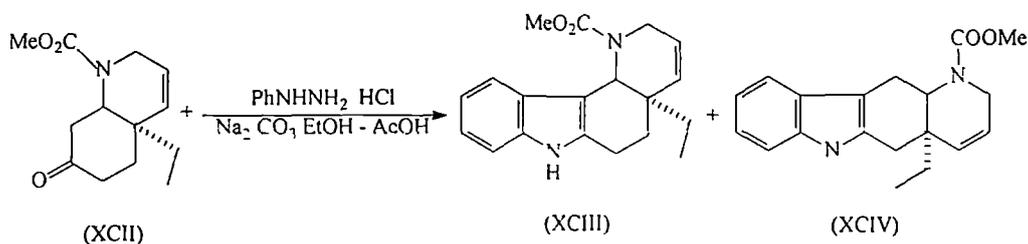


Similarly indoles (LXXXVI–XCI) were obtained from the corresponding ketones (LXXXI, LXXXIV and LXXXV)²⁸ as shown below:



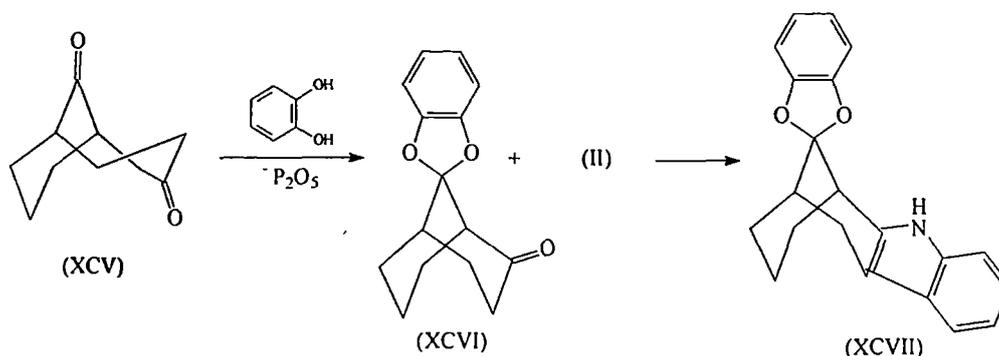


Kozimin *et al.*²⁹ have reported the indolization from ketone (XCII) on reaction with phenylhydrazine in presence of sodium bicarbonate, acetic acid and alcohol to give a mixture of products (XCIII) and (XCIV).

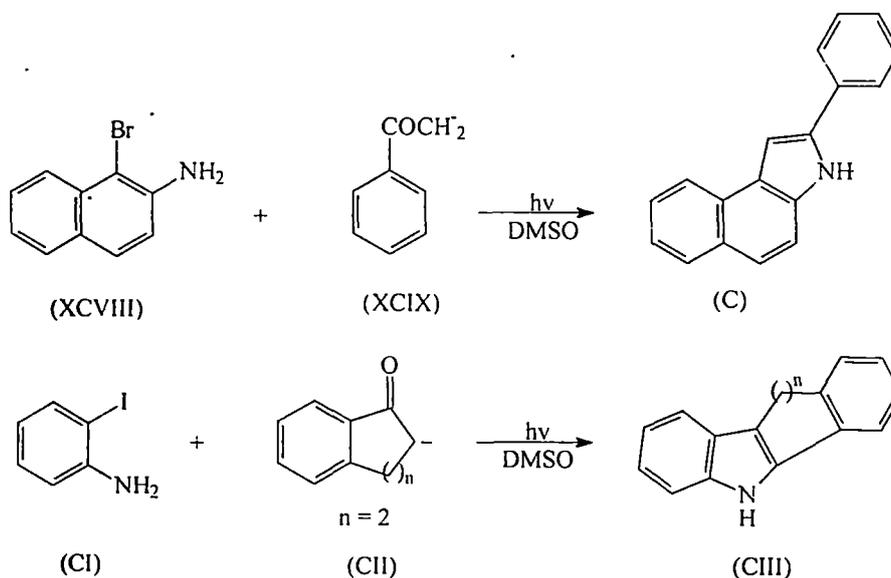


Butkus *et al.*³⁰ have given the synthesis of chiral 1'H-spiro[1,3 benzodioxole-2,12'-(6',10')] methanocyclooct(b) indole (XCVII) a fused polycyclic structure, derived from bicyclo [3.3.1] nonane (XCV). The preparation of mono acetate (XCVI) was accomplished by regioselective protection of the carbonyl group at position C-9 in diketone (XCV) by a reaction with benzene-1,2-diol. Reaction of the monoacetal

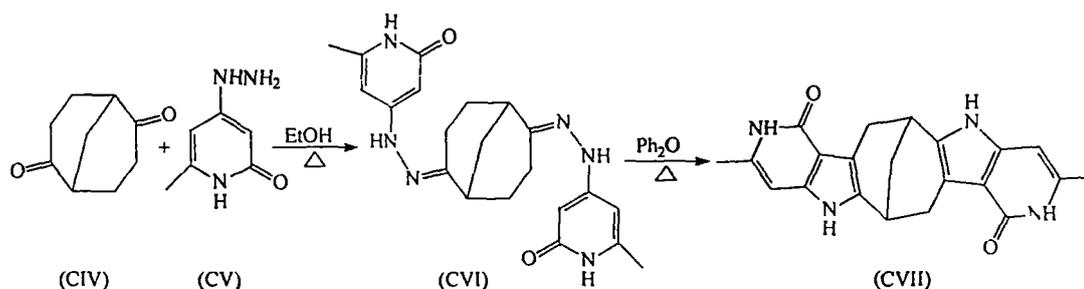
(XCVI) with phenylhydrazine in the presence of catalytic amount of hydrochloric acid afforded indole derivative (XCVII) in excellent yield²⁹.



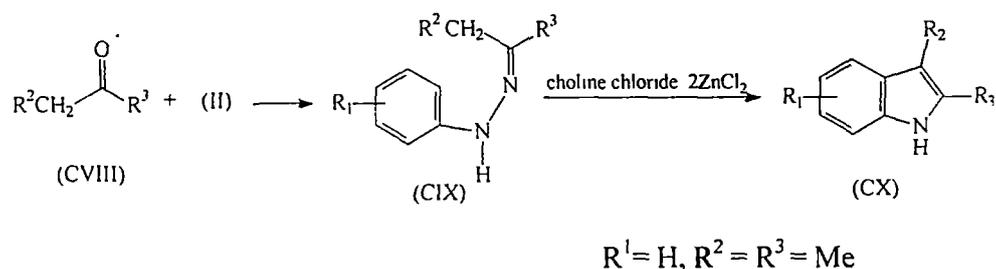
Barolo *et al.*³¹ have reported the synthesis of 2-substituted Indole (C) by reaction of 1-halo-2-naphthalen-2-ylamine (XCVIII) with enolate ion of acetophenone (XCIX). O-Iodoaniline (CI) with 2-indanone anion (CII) afforded 5,10-dihydroindeno[1,2-b] indole (CIII).



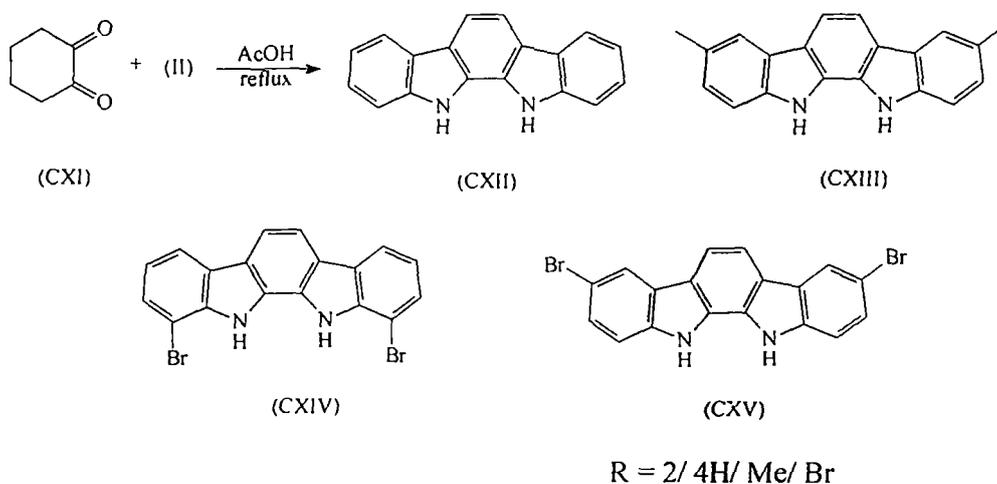
Stoncius *et al.*³² have reported the Fischer indole synthesis of methanocycloocta [1,2-b:5,6-b']-diindole (CVII) from bicyclo[3.3.1]nonane-2,6-dione (CIV) with hydrazine (CV) in refluxing ethanol.



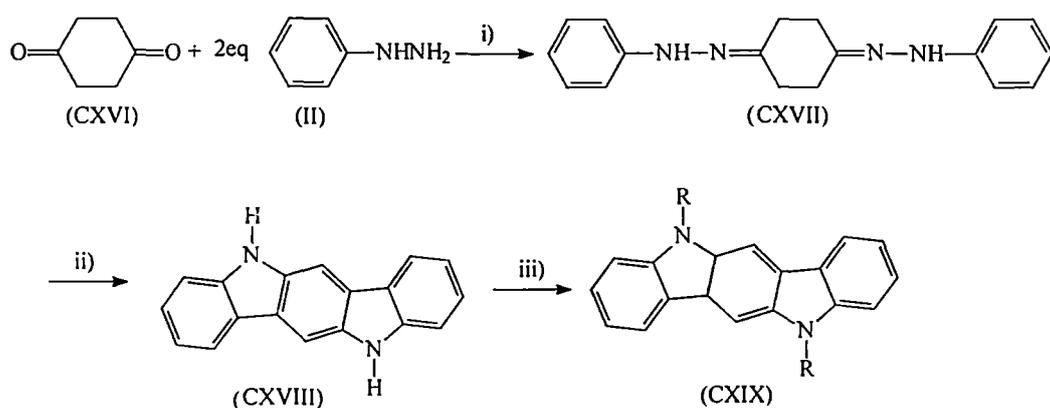
The Fischer indole synthesis occur in high yield with one equivalent of the ionic liquid cholinechloride 2ZnCl_2 . Exclusive formation of 2,3-disubstitutedindole (CX) is observed in the reaction of alkyl methyl ketone (CVIII) with phenylhydrazine (II) and the product readily sublime directly from ionic liquid.³³



Curiel *et al.*³⁴ have reported the synthesis of a family of simple indolo [2,3-a] carbazoles (CXII-CXV) and demonstrated their ability to recognize and sense anions using fluorescence spectroscopy.



Yiliang Wu *et al.*³⁵ have reported indolo[3,2-b]carbazole based thin-film transistor with high mobility and stability. Treatment of 1,4-cyclohexanedione (CXVI) with phenylhydrazine (II) gave cyclohexane-1,4-dione bis-(phenylhydrazone) (CXVII). It is treated with conc sulphuric acid to give indolo [3,2-b]carbazole (CXVIII) which reacts with 1-bromooctane and benzyltriethyl ammonium chloride in DMSO to afford 5,11-disubstituted indole (CXIX).

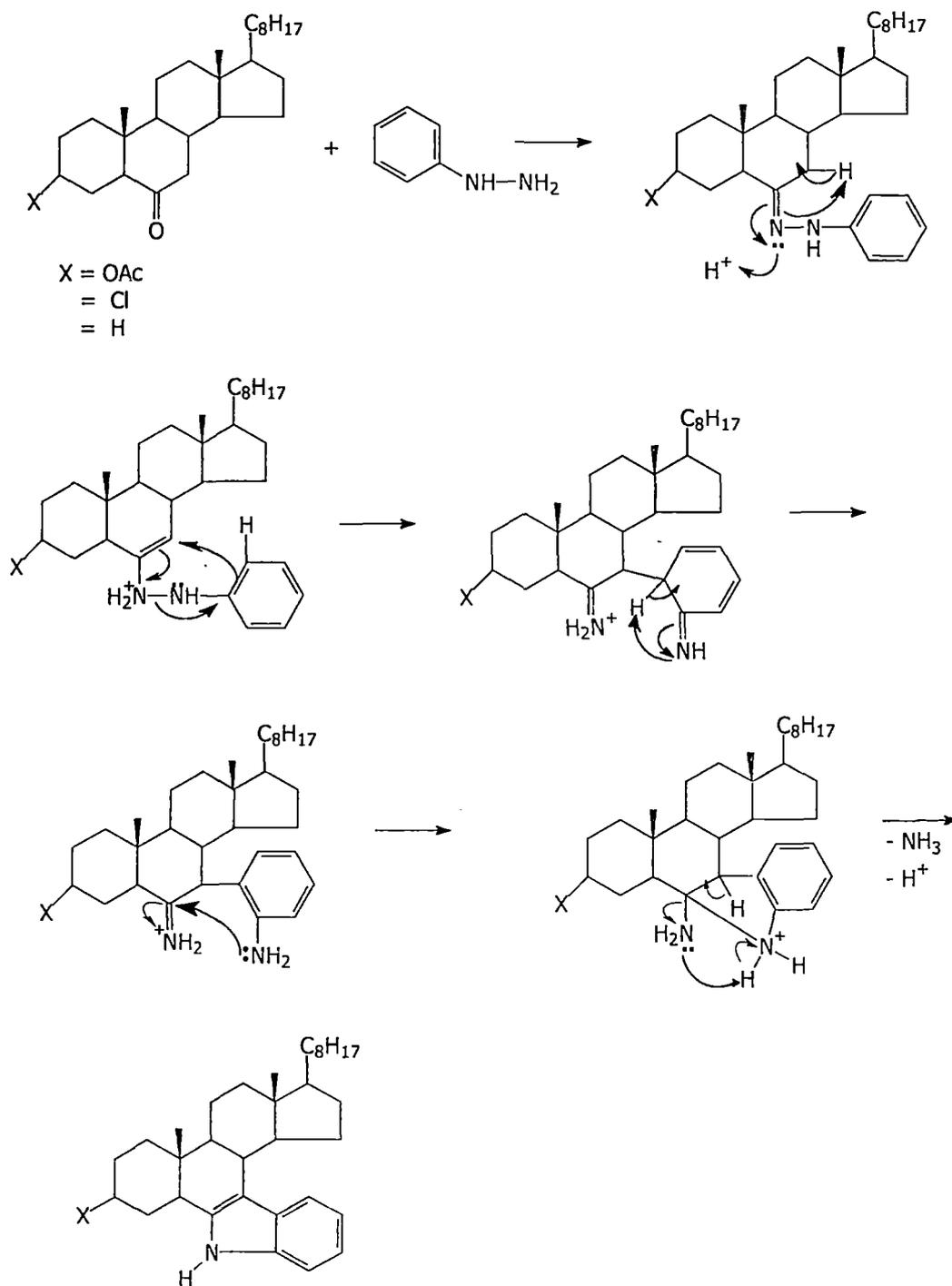


R = octyl /4-octylphenyl /4-methylphenyl

Reagent and conditions

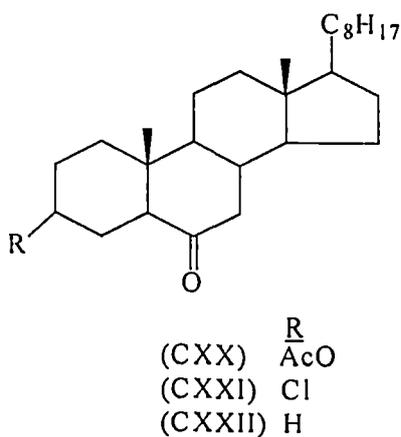
- i) AcOH/ EtOH 50°C
- ii) Conc H₂SO₄
- iii) (a) 1-bromooctane, NaOH, Benzyltriethylammonium chloride DMSO
(b) 1-iodo-4-octyl benzene, 12-crown-6, Cu, 1,2-dichlorobenzene
(c) 4-iodotoluene, 12-crown-6. Cu, 1,2-dichloro benzene.

Proposed Mechanism: The conversion of X to (CXIXa) on the basis of such conversions reported in literatur.⁶



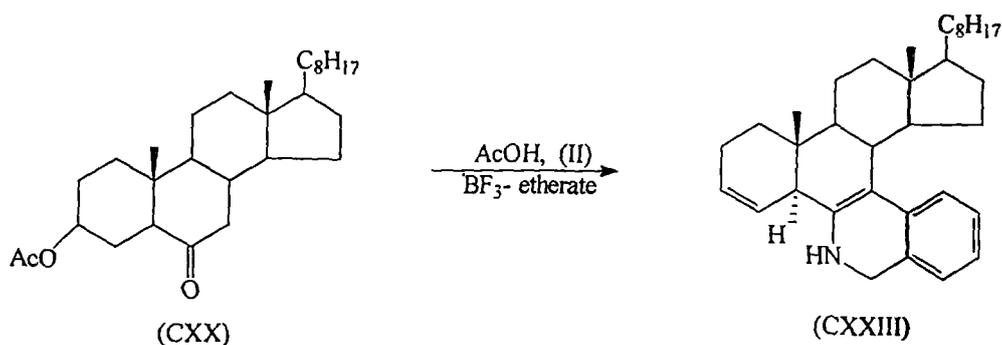
Discussion

Recent survey of literature on indole shows that it has been used on manufacture of pharmaceutical intermediate in alkaloids synthesis³⁶. Various physiological / biological³⁷⁻⁴⁰ activities are influenced by them. These compounds are found to possess antitumor⁴¹⁻⁴², antifungal⁴³, anti-HIV metabolites⁴⁴, antibacterial and antimycotic⁴⁵, antiproliferative⁴⁶, anticancer⁴⁷ and serotonin activities⁴⁸ in association with other physiological activities. With this interest a number of indole synthesis have appeared in literature as reviewed. Further literature reveals that steroidal indoles^{43,28} have also been prepared and show biological activities²⁴. The number of such steroidal indoles is not very high in the reported literature and our continued interest⁴⁹ in the synthesis of modified steroids prompted us to prepare some more such derivatives which can be screened for biological potentials. The present work deals with the synthesis of steroidal indole from easily accessible steroidal ketones such as 3 β -acetoxy-5 α -cholestan-6-one (CXX) 3 β -chloro-5 α -cholestan-6-one (CXXI) and 5 α -cholestan-6-one (CXXII). It is indeed gratifying that these indoles are obtained in good yields and the products obtained have been characterized on the basis of their physical, chemical and spectral studies.



Reaction of 3 β -acetoxy-5 α -cholestan-6-one (CXX) with phenylhydrazine (II) in acetic acid: 5 α -cholestan-3,6-diene[6,7-b] indole (CXXIII).

The ketone (CXX) was taken in glacial acetic acid heated to boiling and phenylhydrazine was added gradually over a period of 45 minutes with small amount of BF₃-etherate as catalyst. The reaction mixture was heated under reflux for four hours. After the completion of the workup, removal of solvent and elution from silica column gave pure compound (CXXIII) as an oil (A) which failed to crystallize.

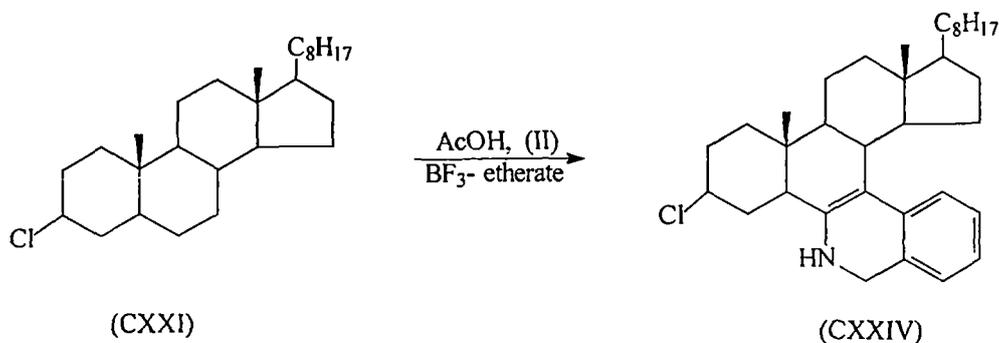


Characterization of compound as 5 α -cholesta-3,6 diene [6,7-b] indole (CXXIII)

The compound oil analysed for C₃₄H₄₉N indicating that the reagent phenylhydrazine is incorporated. The IR spectrum of the compound exhibited bands at 1650, 1618 and 1640 cm⁻¹ indicate the presence of vinylic group, 3061 (C-H stretch aromatic) and 3160-3440cm⁻¹ (-NH). These values indicated the presence of indole moiety attached with steroidal nucleus. On the basis of the mechanism and the IR values the compound can be formulated as (CXXIII) this finds support from ¹HNMR spectrum of the compound which gave peak at δ 7.5 to 6.8 as multiplets for four protons (aromatic), a broad doublet for one proton observed at δ 7.9-7.7 can be assigned to (-NH) proton. A multiplet at δ 3.8 was assigned to C₃- α H (W_{1/2}=16Hz, axial), a broad singlet at δ 2.2 for C₅- α H. Methyl protons were observed at δ 1.0, 0.94, 0.85 and 0.76. On the basis of above evidence, the compound can best be formulated as 5 α -cholesta-3,6-diene- [6,7-b] indole (CXXIII).

Reaction of 3 β -chloro-5 α -cholestan-6-one (CXXI) with phenylhydrazine (II) in acetic acid: 3 β -chloro-5 α -cholestan-6-one [6,7-b] indole (CXXIV).

The ketone (CXXI) was treated with phenylhydrazine (II) in the presence of glacial acetic acid as described earlier after the completion of the work up, removal of solvent and elution from silica column gave pure compound (CXXIV) which also failed to crystallize.

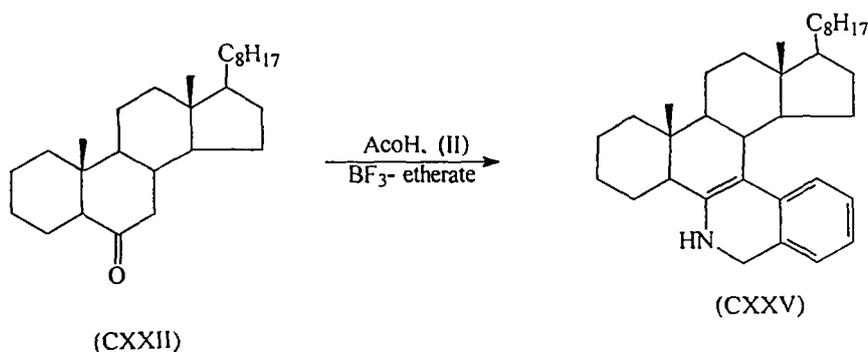


Characterization of compound oil (B) as 3 β -chloro-5 α -cholestan-6-one [6,7-b] indole (CXXIV).

The compound was analysed for $C_{34}H_{50}NCl$ indicating that the reagent phenylhydrazine (II) is incorporated. The I.R. spectrum of the compound exhibited band at 3439 (-NH) 1622 (C=C), 3150-3070 (C-H, stretch aromatic). 1645 (aromatic) and 715 (C-Cl) cm^{-1} . These values indicate the presence of indole moiety, attached with steroidal nucleus. On the basis of the mechanism and their value the compound can be formulated as (CXXIV) this finds support from 1H NMR spectrum of the compound which gave peak at δ 7.5 to 6.8 as the multiplets for four protons (aromatic) A singlet for one proton observed at δ 4.7 can be assigned to (-NH) proton. A multiplet at δ 3.8 was assigned to $C_3-\alpha H$ ($W_{1/2} = 16Hz$ axial), a singlet at δ 2.2 for $C_3-\alpha H$ proton and a singlet at δ 2.0 for C_8-H proton also observed. / Other methyl protons were observed at δ 1.2, 1.0, 0.97 and 0.85. On the basis of above evidences the compound can best be formulated as 3 β -chloro-5 α -cholestan [6,7,-b]indole (CXXIV).

Reaction of 5 α -cholestan-6-one (CXXII) with phenylhydrazine (II) in acetic acid: 5 α -cholestano [6,7-b] indole (CXXV)

The ketone (CXXII) was reacted with phenylhydrazine (II) in the presence of acetic acid as earlier described. After the completion of the workup, removal of the solvent and elution from silica column gave pure compound (CXXIV) as an oil (C) failed to crystallize.



Characterization of compound oil (C) as 5 α -cholestano [6,7-b] indole (CXXV)

The compound oil (C) was analysed for $C_{34}H_{51}N$ indicating that the reagent phenylhydrazine (II) is incorporated. The IR spectrum of the compound exhibited band at 3053 (C-H, stretch aromatic), 1609-1592 (C=C aromatic) and 3481cm^{-1} (-NH). These values indicates the presence of indole moiety attached with the steroidal nucleus. On the basis of the mechanism and the IR values the compound can be formulated as (CXXV). This find support from $^1\text{HNMR}$ spectrum of the compound which gave peak at $\delta 7.6, 7.5, 7.3$ and 7.1 m (4H aromatic protons). A broad singlet for one proton observed at $\delta 3.8$ can be assigned to (-NH) proton. A multiple band at $\delta 2.81$ assigned to C_5 - α H proton, and also give a multiple band at $\delta 2.2$ (C_8 -H). Other methyl protons were observed at $\delta 1.1, 0.91, 0.86$ and 0.62 . On the basis of above evidence the compound has been identified as 5 α -cholestano [6,7-b] indole (CXXV).

Experimental

All the melting points are uncorrected infrared spectra (I.R.) were measured in KBr with Perkin-Elmer 237 and Unicem SP 300 spectrophotometers. The I.R. value are given in cm^{-1} (s-strong m-medium w-weak br-broad). $^1\text{HNMR}$ spectra were run in CDCl_3 on Varian A60 instrument and $^1\text{HNMR}$ values were given in ppm (s-singlet d-doublet t-triplet b-broad m-multiplet centred at). TMS as internal standard thin layer chromatography plates were coated with silica gel G and developed in an iodine chamber light petroleum refers to fraction b.p. $60-80^\circ$.

3 β -Chlorocholest-5-ene (CXXVI)

Freshly purified thionyl chloride (75ml) was added gradually to cholesterol (100g) at room temperature a vigorous reaction ensued with the evolution gaseous product. When the reaction slacked, the reaction mixture was gently heated at the temperature of $50-60^\circ$ on a water bath for 1hr and than poured on the crushed ice-water, mixture with stirring. The yellow solid obtained was filtered under suction and washed several times with ice-cold water and air dried recrystallization of crude product from acetone gave 3 β -chlorocholest-5-ene (95.5gm) (CXXVI). m.p. $95-96^\circ$ (reported⁵⁰ $96-97^\circ$). It gave positive Beilstein test and a yellow colour with tetraanitromethane in chloroform.

3 β -Acetoxycholest-5-ene (CXXVII)

A mixture of cholesterol (50g) pyridine (75ml freshly prepared over KOH) and freshly distilled acetic anhydride (50ml) was heated on water bath for two hours. The resulting brown solution was poured into crushed ice-water mixture with stirring. A light brown solid was obtained which filtered under suction washed with water until free from pyridine and air dried. The crude product on recrystallization from acetone gave pure 3 β -acetoxycholest-5-ene (45.0g) (CXXVII), m.p. 112° (reported⁵¹ m.p. 113°).

Cholest-5-ene (CXXVIII)

3 β -Chlorocholest-5-ene (15g) was dissolve in warm amyl alcohol (300ml) and sodium metals (35.0g) was added in small portion to the solution with continuous stirring over a period of eight hours. The reaction mixture was heated now and then during the course of reaction in order to keep the sodium metal dissolve the reaction

was poured into water acidify with HCl and allowed to stand over night a white crystalline solid was obtained which was filtered under suction and washed thoroughly with water and air dried recrystallization of the crude materials from acetone gave cholest-5-ene in cubes (10.8g) (CXXVIII), m.p. 93° (reported⁵⁰ m.p. 89.5-91.2°).

3β-Chloro-6-nitrocholest-5-ene (CXXIX)

To a well stirred mixture of 3β-chlorocholest-5-ene (12g) glacial acetic acid (80ml) and nitric acid (25ml d1.52) at 20°C was added sodium nitrite (3.0g) gradually. After the complete addition of sodium nitrite the mixture was further stirred for 1hr the ice-cold water (200 ml) was added and the yellowish solid thus separated was filtered and air-dried. The desired product was recrystallized from ethanol as needles (9.0g) (CXXIX), m.p. 150-152° (reported⁵⁰ m.p. 149°).

3β-Acetoxy-6-nitrocholest-5-ene (CXXX)

To a mixture of 3β-acetoxycholest-5-ene (10.0g) and a nitric acid (250ml d1.42), sodium nitrite (10.0g) was gradually added over a period of one hour. With continuous stirring slight external cooling was also applied during the course of reaction and stirring was continued for 2 hours. When a yellow spongy mass separated on the surface of the mixture. The mixture was then diluted with cold water (200ml) when a green coloured solution was obtained the whole mass was extracted with ether and the ethereal solution was successively washed with water and sodium bicarbonate (NaHCO₃) solution (5%) until (the washing attain pink colour) and again washed with water and air dried over anhydrous sodium sulphate. Removal of the solvent afforded as an oil which was crystallized from methanol (7.2g), m.p. 104° (reported⁵⁰ m.p. 103-104°).

6-Nitrocholest-5-ene (CXXXI)

A suspension of finely powdered cholest-5-ene (6.0g) in glacial acetic acid (50ml) was vigorously stirred at room temperature and treated slowly with nitric acid (15ml, 1.5) followed by the addition of sodium nitrite (3g) over a period of 1 hour. The reaction mixture was poured into cold water and the yellow product thus obtained was extracted with ether. The ethereal solution was successively washed

with water, sodium bicarbonate (NaHCO_3) solution (5%) (until the washing attain pink colour) and again washed with water. Removal of the solvent after drying over anhydrous sodium sulphate provided as an oil which was crystallized from ethanol in leafplets (4.0g), m.p 119-120° (reported⁵² m.p 120-121).

3 β -Chloro-5 α -cholestan-6-one (CXXI)

A solution of 3 β -chloro-6-nitrocholest-5-ene and glacial acetic acid (240ml) was heated just to get a clear solution. To this zinc dust (24g) was added gradually in small portion with constant shaking. The suspension was heated under reflux for four hours and water (24ml) was added at regular interval during the course of reaction. The hot solution was poured into ice-cold water. The organic matter was extracted with ether and ethereal solution was washed successively with water, sodium bicarbonate (NaHCO_3) solution (5%) and again with water and dried over sodium sulphate (anhydrous). Evaporation of the solvent furnished the ketone as an oil which was crystallized from methanol (8.7g) (CXXI), m.p 128-129° (reported⁵⁴ m.p. 129°).

3 β -Acetoxy-5 α -Cholestan-6-one (CXX)

Nitro compound (CXXX) (6.0g) was dissolved in glacial acetic acid (250ml) and zinc dust (12.0) gm was added in small portion with shaking. The suspension was heated under reflux for four hours water (12ml) was added during the course of reaction. The hot solution was filtered, cool to room temperature and diluted with large excess of water. The precipitate thus obtained was taken in ether and ethereal solution was washed with water sodium bicarbonate (NaHCO_3) solution (10%) water and dried over sodium sulphate (anhydrous). Removal of the solvent gave an oil which was crystallized from methanol (3.9g) (CXX), m.p. 122° (reported⁵⁵ m.p. 127-128°).

5 α -Cholest-6-one (CXXII)

6-Nitrocholest-5-ene (CXXXI) (6.0g) was dissolve in glacial acetic acid (200ml) by heating and to this solution zinc dust (12.0g) was added in small portion. After the initial exothermic reaction had subsided the suspension was heated under reflux for three hours and water (12ml) was added gradually during the course of reaction the

solution was then filtered and the residue was washed with two (10ml) portion of warm acetic acid. To the filtrate a few ml of water was added till turbidity developed and it was allowed to stand overnight at room temperature. The crystalline material thus separated was filtered under suction and washed thoroughly with water in order to remove zinc acetate. The organic solid was air dried and then recrystallized from ethanol (3.6g) (CXXII), m.p. 96-90° (reported⁵⁶ m.p. 95-96°).

Reaction of 3 β -acetoxy-5 α -cholesan-6-one (CXX) with phenylhydrazine in acetic acid: 5 α -cholestano-3,6-diene[6,7-b]indole (CXXIII).

The ketone (CXX: 300mg; 0.67mmol) was taken in glacial acetic acid (25ml) heat it boil and phenylhydrazine (375mg; 2.40mmol) was added gradually with in 45 minutes. During this period the colour changed from colourless to red. The reaction mixture was heated under reflux for four hours with stirring, small amount of BF₃-etherate was added as catalyst. The progress of the reaction was monitored by TLC. After the completion of the reaction, the solvent was removed under the reduced pressure and the residue thus obtained was extracted with ether. The ethereal layer washed with several times with water and sodium bicarbonate (NaHCO₃) solution (5%) and dried over anhydrous sodium sulphate. Removal of the solvent gave oil (A) (250mg; 0.53mmol) (CXXIII) which was chromatographed over silica gel 40 g.

5 α -cholestano-3,6-diene[6,7-b]indole (CXXIII)

Elution	: Pet. ether: ether (10:1) yield (170mg; 0.36mmol)
IR	: λ_{\max} 1650, 1618-1640 cm ⁻¹ (C=C-C=C-) 3061 (C-H stretch aromatic) and 3160-3440cm ⁻¹ (-NH)
¹ HNMR (CDCl ₃)	: δ 7.5 to 6.8 m (4H aromatic protons), δ 7.9-7.7 (NH) δ 3.8 [(1H C ₃ - α H W _{1/2} =16Hz axial)], δ 2.2 br (C ₅ - α H). δ 1.0, 0.94, 0.85 and 0.76 (other methyl protons).
Analysis found	: C; 83.74, H; 11.63 N; 3.27
C ₃₆ H ₅₃ NO ₂ requires	: C; 83.9, H; 11.89, N; 3.29%

On the basis of TLC, IR and ¹HNMR values found identical the compound is characterized as cholesta-3,6-diene[6,7-b] indole (CXXIII).

Reaction of 3β-chloro-5α-cholestan-6-one (CXXI) with phenylhydrazine in acetic acid: 3β-chloro-5α-cholestano [6,7-b] indole (CXXIV)

3β-Chloro-5α-cholestan-6-one (CXXI:250mg:0.61mmol) was taken in glacial acetic (30ml) heat to boil and Phenylhydrazine (300mg: 2.07mmol) was added gradually with in 45 minutes. During this period the colour changed from colourless to red the reaction mixture was heated under reflux for four hours. with stirring. Small amount of BF₃-etherate was added as catalyst. The progress of the reaction was monitored by TLC. After the completion of the reaction, the solvent was removed under reduced pressure and the residue thus obtained was extracted with ether. The ethereal layer washed with several times with water and sodium bicarbonate (NaHCO₃) solution (5%) and dried over anhydrous sodium sulphate removal of the solvent gave semi solid (190mg:0.37mmol) which was chromatographed over silica gel.

3β-Chloro-5α-cholestano [6,7-b] indole (CXXIV) as oil (B)

Elution	:	Pet ether : ether (15:1) yield (100mg: 0.19mmol)
IR	:	3439 (-NH) 1622 (C=C), 3150-3070 (C-H, stretch aromatic), 1645 (aromatic) and 715 (C-Cl) cm ⁻¹
¹ HNMR (CDCl ₃)	:	δ 7.5 to 6.8 m(4H aromatic protons), δ4.7 s(-NH), δ3.8(3α-HW ^{1/2} =16Hz axial), δ2.28 m(C ₅ Protons and δ2.0 for (C ₈ -protons). δ 0.85, 1.2, 0.97 and 1.0 (other methyl protons).
Analysis found	:	C; 81.50, H; 10.45, N; 5.72
C ₃₄ H ₅₀ NCl requires	:	C; 81.41, H; 10.26, N; 5.43%

On the basis of TLC, IR and ¹HNMR values found identical the compound is characterized as 3β-chloro-5α-cholestano [6,7-b] indole (CXXIV).

Reaction of 5 α -Cholestan-6-one (CXXII) with phenylhydrazine in acetic acid:

5 α -cholestano [6,7-b] indole (CXXII)

5 α -Cholestan-6-one (CXXII: 350mg: 0.91mmol) was taken in glacial acetic acid (30ml) heat to boil and phenylhydrazine (400mg: 2.77mmol) was added gradually with in 45 minutes. During this period the colour changed from colourless to red. The reaction mixture was heated under reflux for four hours with continue stirring. Small amount of BF₃-etherate was added as catalyst. The progress of the reaction was monitored by TLC After the completion of the reaction, the solvent was removed under reduced pressure and the residue thus obtained was extracted with ether. The ethereal layer washed with several times with water and sodium bicarbonate (NaHCO₃) solution (5%) and dried over anhydrous sodium sulphate. Removal of the solvent gave oil (290mg: 0.61mmol) which was chromatographed over silica gel.

5 α -Cholestano [6,7-b] indole (CXXV) as oil (C)

Elution : Pet. ether

Yield : (110mg: 0.23mmol)

IR : 3053 (C-H, stretch aromatic), 1609-1592 (C=C aromatic) and 3481 cm⁻¹ (-NH)

¹HNMR (CDCl₃) : δ 7.6, 7.5, 7.3 and 7.1 m(4H aromatic protons),
 δ 3.8 br (-NH), δ 2.81 m(C₅ α -H), δ 2.28 m(C₈-H).
 δ 1.1, 0.91, 0.86 and 0.62 (other methyl protons).

Analysis found : C; 86.21, H; 10.72, N; 3.13.

C₃₄H₅₁N requires : C; 86.11, H; 10.27, N; 3.11%

On the basis of TLC, IR and ¹HNMR found identical the compound (CXXV) was characterized as 5 α -cholestano [6,7-b] indole.

References

1. A. Baeyer; *Ann.*, 140, 295 (1886).
2. E. Fischer and F. Jourden; *Ber.*, 16, 2241 (1883).
3. E.W. Warnhoff and P. Nanonggai; *J. Org. Chem.*, 27, 1186 (1962).
4. Y. Ban and Y. Sato; *Chem. Pharm. Bull.*, 1186 (1962) Tokyo. 13, 1073 (1965).
5. B. Robinson; *Chem. Rev.*, 63, 227 (1969).
6. Robinson, B; The fisher indole synthesis; John Willey and Sons, New York, NY, 1982 (Review).
7. T. Sugawara, M. Adachi, K. Sasakura and A. Kitagawa; *J. Org. Chem.*, 44, 578 (1979).
8. M.P. Irismetov, M.I. Goryaev, T.V. Rivkina; (Inst. Khim. Nauk. Alma-Ata. USSR); *Izv. Akad. Nauk Kaz. SSR, Serkhim.*, 3, 60 (1979).
9. P.A. Wender and A.W. White; *Tetrahedron Letter.*, 22, 1475 (1981).
10. W. Madelung; *Ber. Dtsch. Chem. Ges.*, 45, 1128 (1912).
11. W.J. Houlihan, V.A. Parrino and Y. Uike; *J. Org. Chem.*, 46, 4511 (1981).
12. J.L. Bernier and J.P. Henichart; *J. Org. Chem.*, 46, 4197 (1981).
13. P.A. Wender and A.W. White; *Tetrahedron.*, 39, 3767 (1983).
14. A.B. Smith, III, J.K. Wood, T. Leenay, E.G. Nolen and T. Sunazuka; *J. Am. Chem. Soc.*, 114, 1430 (1992).
15. J. Graham, A. Ninan, K. Reza, M. Sainsbury and H.G. Shertzer; *Tetrahedron.*, 48, 167 (1992).
16. K. Maruoka, M. Oishi and H. Yamamoto; *J. Org. Chem.*, 58, 7638 (1993).
17. J. Gracia, N. Casamitjana, J. Bonjoch and J. Bosch; *J. Org. Chem.*, 59, 3939 (1994).
18. L. Rao and A.K. Mukerjee; *Ind. J. Chem.*, 33B, 166 (1994).

19. J. Bonjoch, J. Catena and N. Valls; *J. Org. Chem.*, 61, 7106 (1996).
20. M. Murugesan and K. Kaniappan; *Ind. J. Chem.*, 36B, 83 (1997).
21. S. Atarashi, J.K. Choi, D.C. Ha, D.J. Hart, D. Kuzmich, C.S. Lee, S. Ramesh and S.C. Wu; *J. Am. Chem. Soc.*, 119, 6226 (1997).
22. D.W. Brown, M.F. Mahon, A. Ninan and M. Sainsbury; *Perkin Trans-1*, 1699 (1997).
23. C. Chen, D.R. Lieberman, R.D. Larsen, T.R. Verhoeven and P.J. Reider; *J. Org. Chem.*, 62, 2676 (1997).
24. D.W. Brown, M.F. Mahon, A. Ninan and M. Sainsbury; *Perkin Tans-1*, 2329 (1997).
25. S. Wagaw, B.H. Yang and S.L. Buchwald; *J. Am. Chem. Soc.*, 120, 6621 (1998).
26. S. Wagaw, B.H. Yang and S.L. Buchwald; *Ibid.*, 121, 10251 (1999).
27. K. Cucek and B. Vercek; *Synlett.*, 1, 120 (1999).
28. H.J. Finlay, T. Honda and G.W. Gribble; *Arkivoc.*, (XII), 38 (2002).
29. S.A. Kozmin, T. Iwama, Y. Huang and V.H. Rawal; *J. Am. Chem.Soc.*, 124, 4628 (2002).
30. E. Butkus, M. Jule and S. Stoncius; *Org. Biomol. Chem.*, 1, 391 (2003).
31. S.M. Barolo, A.E. Lukach, and R.A. Rossi; *J. Org. Chem.*, 68, 2807 (2003).
32. S. Stoncius, E. Butkus, A. Zilinskas, K. Larsson, L. Ohrstrom, U. Berg and K. Warnmark; *J. Org. Chem.*, 69, 5196 (2004).
33. R.C. Morales, V. Tambyrajah, P.R. Jenkins, D.L. Davies and P. Andrew *Chem. Communication.* 158 (2004).
34. D. Curiel, A. Cowley and P. D. Beer; *Chem. Communication.*, 236 (2005).
35. Y. Wu, Y. Li, S. Gardner and B.S. Ong; *J. Am. Chem. Soc.*, 127, 614 (2005).

36. G.W. Gribble; *J. Chem. Soc. Perkin Trans. I.*, 1045 (2000).
37. S. Yuichi, S. Atsushi, K. Tetsuya, S. Atsushi, O. Satoshi, O. Hisashi and O. Osamu; *Bioorg. and Med. Chem. Lett.*, 16, 3569 (2006).
38. R.E. Beevers, G.M. Buckley, N. Davies, J. L. Fraser, F.C. Galvin, D. R. Hannah, A.F. Haughan, K. Jenkins, S.R. Mack, W.R. Pitt, A.J. Ratcliffe, M.D. Richard, V. Sabin, A. Sharpe and S.C. Williams; *Bioorg. and Med. Chem. Lett.*, 16, 2535 (2006).
39. R.K. Tiwari, A.K. Verma, A.K. Chhillar, D. Singh, J. Singh, V.K. Sankar, V. Yadav, G.L. Sharma and R. Chandra; *Bioorg. and Med. Chem.*, 14, 2747 (2006).
40. L.W. Schenek, K. Kuna, W. Frank, A. Albert, C. Asche and U. Kucklaender; *Bioorg. and Med. Chem.*, 14, 3599 (2006).
41. A. Molina, J.J. Vaquero, J.L. Gracia-Navio, J.A. Builla, B.P. Teresa, F. Gago, M.M. Rodrigo and M. Ballesteros; *J. Org. Chem.*, 61, 5587 (1996).
42. C.H. Nguyen, C. Marchand, D. Stephane, S. Jian.Sheng, T. Garestier, C. Helene, and E. Bisagul; *J. Am. Chem. Soc.*, 120, 2501 (1998).
43. A. Park, R. E. Moore and G.M.L. Patterson; *Tetrahedron Letter.*, 33, 3257 (1992).
44. K.M. Meragelman, L.M. West, P.T. Northcote, L.K. Pannell, T.C. Mckee and M.R. Boyd; *J.Org. Chem.*, 67, 6671 (2002).
45. R.E. Moore, C. Chenk, G.Y. Xu-Qiang and G.M.L. Patterson; *J. Org. Chem.*, 52,1036 (1987).
46. C. Marminon, A. Pierre, B. Pfeiffer, V. Pe'rez, S. Le'once and A. Joubert; *J. Med. Chem.*, 46, 609 (2003).
47. J.T. Kuethe, A. Wong, C. XiangQ, J. Smitrovich, I.W. Davies and D.L. Hughes; *J. Org. Chem.*, 70, 5528 (2005).
48. A.H. Schmidt and P. Eilbracht; *J. Org. Chem.*, 70, 5528 (2005).

49. Shafiullah, Hasrat Ali and M. Rafiuddin Ansari; *J. Ind. Chem. Soc.*, LVIII (1981).
50. R.H. Baker and E.N. Squire; *J. Am. Chem. Soc.*, 70, 1487 (1948).
51. C.E. Anagostopoulos and L.F. Fieser; *J. Am. Chem. Soc.*, 76, 532 (1954).
52. W.G. Dauben and K.H. Takemura; *J. Am. Chem. Soc.*, 75, 6302 (1953).
53. A. Winduans; *Chem. Ber.*, 52, 162 (1920).
54. R.M. Dason and B. Reigel; *J. Org. Chem.*, 13, 424 (1948).
55. A. Windaus and O. Dalmer; *Chem. Ber.*, 52, 162 (1919).
56. C.W. Shoppe, D.N. Jones, J.R. Lewis and G.H.R. Summers; *J. Chem. Soc.*, 2876 (1955).