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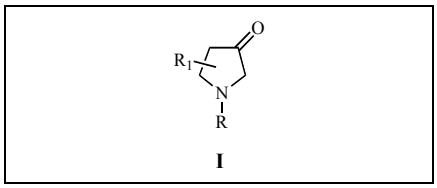

I

This review presents a survey of the synthetic methods and reactions of 3-pyrrolidinones **I** (R = H, alkyl, acyl, ester; R_1 = H, alkyl, cyano, ester, etc). 3-Pyrrolidinones are synthetically versatiles substrate, as they can be used for synthesis of a large variety of heterocyclic compounds, such as indoles and 5-deazapteroic acid analogues and as a raw material for drug synthesis. The high reactivity of an active methylene group next to the carbonyl of the pyrrolidine ring is useful for various syntheses.

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INTRODUCTION

From a synthetic viewpoint, 3-pyrrolidinones occupy an important position in the synthesis of various heterocyclic systems. The Pyrrolidine ring is a component of many alkaloids, many of which display diverse and potent biological activities. Also, they are key building blocks for a wide variety of synthetic targets ranging from biologically active molecules to liquid crystals and conducting polymers. Despite this importance, 3-pyrrolidinones have not been previously reviewed. Several methods for preparation of 3-pyrrolidinones have been reported, including Michael condensation followed by base-catalyzed intramolecular Dieckmann condensation. Also, several reactions belonging to both the carbonyl and active methylene groups are mentioned, finally some main applications of 3-pyrrolidinone compounds are reported.

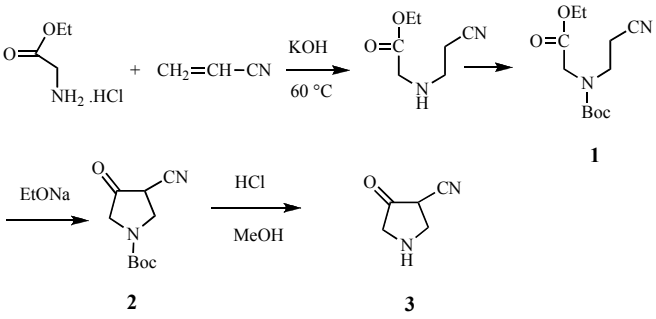
1. SYNTHESIS OF 3-PYRROLIDINONES

Generally, 3-pyrrolidinones are prepared *via* Michael condensation followed by base-catalyzed intramolecular condensation of the Dieckmann type.

1.1. *N*-(Unsubstituted)-3-pyrrolidinones

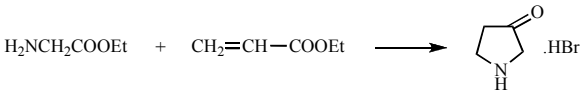
Ethyl glycinate hydrochloride was reacted with acrylonitrile in aqueous KOH at 60 °C, and the resulting Michael adduct was subsequently treated with di-*tert*-butyl dicarbonate to produce protected cyano ester **1**. The ester **1** was smoothly cyclized to the cyano ketone **2** by sodium ethoxide. Treatment of **2** with HCl/MeOH gave 4-cyano-3-pyrrolidinone **3** as depicted in Scheme1 [1].

Scheme 1



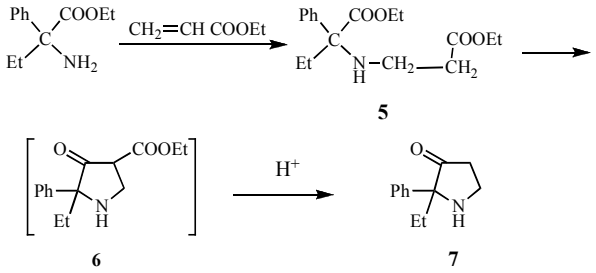
Michael addition of ethyl glycinate to ethyl acrylate followed by Dieckmann condensation and decarboxylation gave 3-pyrrolidinone.HBr **4** (Scheme 2) [2].

Scheme 2



Alkylation of α-ethyl α-phenyl-β-alanine ethyl ester with ethyl chloroacetate afforded the amino diester **8**. Dieckmann condensation of the latter, in the presence of NaH in toluene, yielded 2-carbethoxy-4-ethyl-4-phenylpyrrolidin-3-one **9**, which underwent hydrolysis and decarboxylation upon treatment with dilute HCl to give 4-ethyl-4-phenylpyrrolidin-3-one **10** (Scheme 3) [3].

Scheme 3



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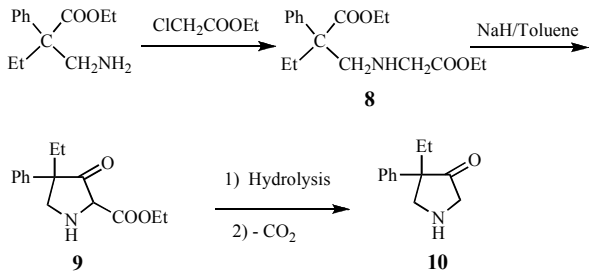
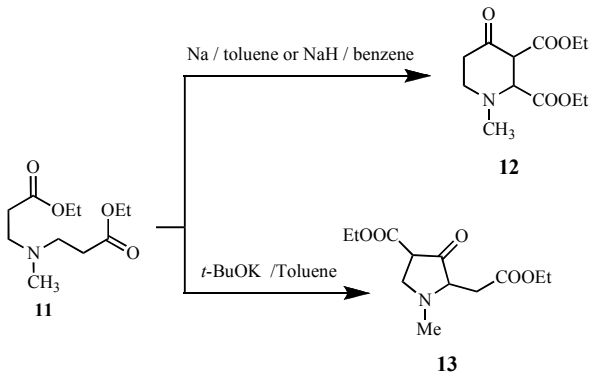
Scheme 4



1.2. Synthesis of *N*-alkyl-3-pyrrolidinones

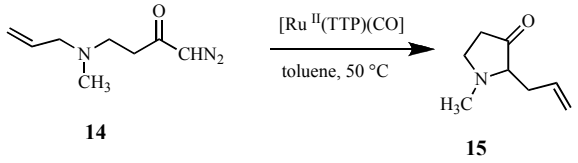
The cyclization of diethyl *N*-(2-carbethoxyethyl)-*N*-methylaspartate **11** using sodium hydride in benzene, sodium in toluene, or sodium ethoxide in ethanol, gave exclusively the six-membered ring product, l-methyl-2,3-dicarbethoxy-4-piperidone **12**. Under non-reversible conditions (potassium *t*-butoxide in toluene at -20°C) l-methyl-2-carbethoxymethyl-4-carbethoxy-3-pyrrolidinone **13** was the primary product (Scheme 5) [4].

Scheme 5



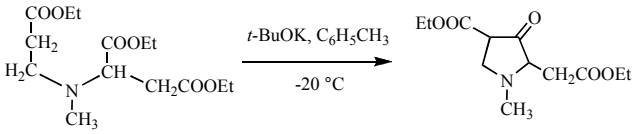
N-Methyl-2-allyl-3-pyrrolidinone **15** was prepared by addition of [Ru^{II}(TTP)(CO)] to diazo compound **14** (Scheme 6) [5, 6].

Scheme 6



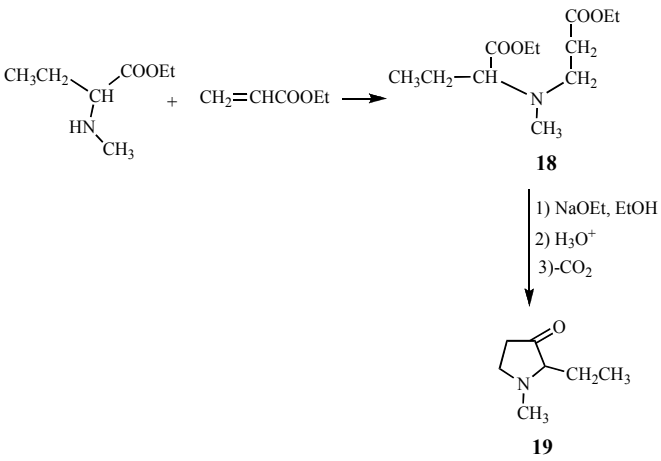
Cyclization of diethyl *N*-(2-carbethoxyethyl)-*N*-methyl-aspartate **16** under non-reversible conditions (*t*-BuOK in toluene at -20 °C) led to 1-methyl-2-carbethoxymethyl-4-carbethoxy-3-pyrrolidinone **17** (Scheme 7) [7].

Scheme 7



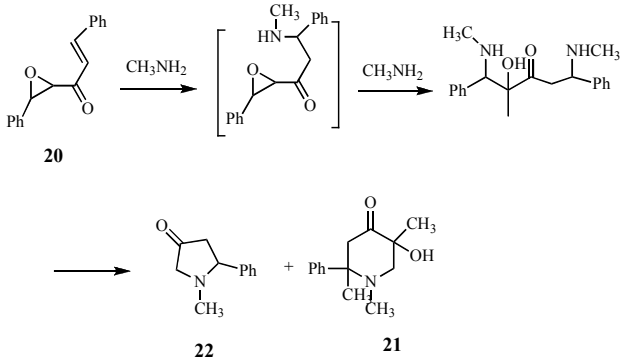
Adding ethyl α-methylaminobutyrate to ethyl acrylate gave the diester **18**. Which upon closure by sodium ethoxide followed by acid hydrolysis and decarboxyaltion gave 2-ethyl-1-methyl-3-pyrrolidinone **19** (Scheme 8) [8].

Scheme 8



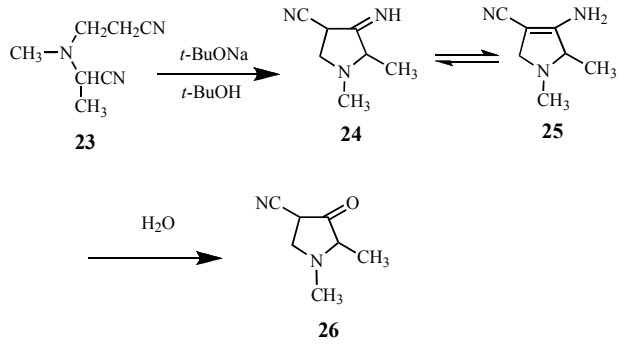
5-Hydroxy-1,2,5-trimethyl-2-phenylpiperidin-4-one **21** and 1-methyl-5-phenylpyrrolidin-3-one **22** were obtained by the reaction of acryloyloxiranes **20** with methylamine (Scheme 9)[9,10].

Scheme 9



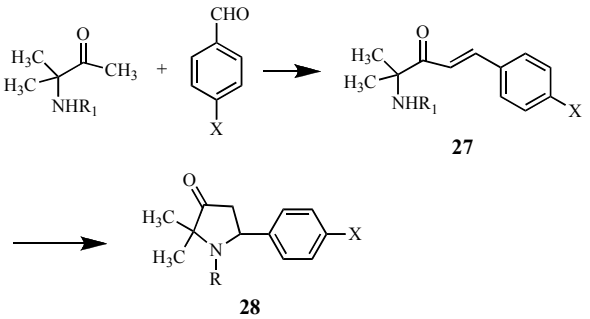
Cyclization of the dinitrile **23** in *t*-butyl alcohol in the presence of a catalytic amount of sodium *t*-butoxide gave the cyclic imino-nitrile **24**, which was present as an enamine **25**. Hydrolysis of this product gave the 3-pyrrolidinone derivative **26** (Scheme 10) [11].

Scheme 10



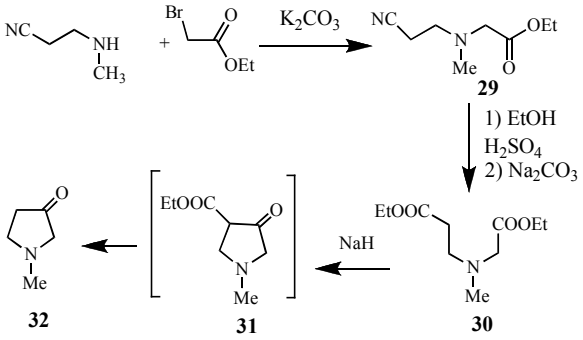
α,β-Unsaturated aminoketones **27**, have been prepared by Claisen-Schmidt condensation of α-aminoketones with aromatic aldehydes. The products where R_4 = H were converted to the corresponding 1,2,2-trialkyl-5-aryl-3-pyrrolidinones **28**, by thermal cyclization (R_1 = CH_3, C_2H_5, iso-C_3H_7., X = H, CH_3, OCH_3, Cl) (Scheme11) [12].

Scheme 11



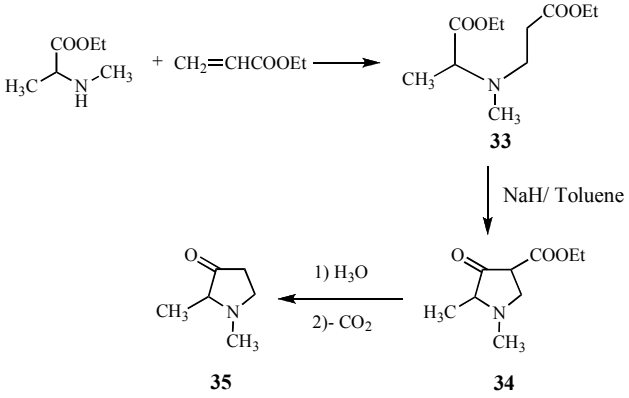
1-Methyl-pyrrolidin-3-one **32** has been prepared by reaction of *N*-methyl-β-alaninonitrile and anhydrous potassium carbonate with ethyl bromoacetate, which afforded [(2-cyano-ethyl)-methyl-amino]-acetic acid ethyl ester **29**, which under further alcoholysis gave the intermediate **30**. Dieckmann condensation of **30** with 60% sodium hydride in anhydrous toluene at 0°C gave 1-methyl-3-oxo-pyrrolidine **32** *via* the intermediate ethyl 1-methyl-4-oxopyrrolidine-3-carboxylate **31** by hydrolysis with 6 *N* HCl (Scheme12) [13,14].

Scheme 12



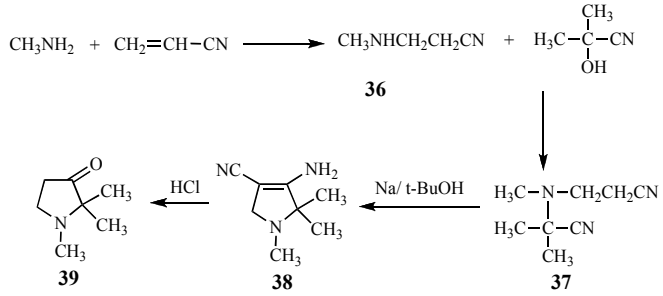
Condensation of ethyl acrylate with α-carbethoxy-ethylmethylamine gave the diester **33**. This upon closure by sodium hydride and toluene gave the keto ester **34**. Acid hydrolysis and decarboxylation of **34** gave 1,2-dimethyl-3-pyrrolidinone **35** (Scheme13) [15].

Scheme 13



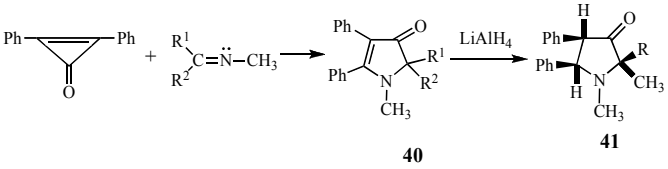
Adding of methylamine to acrylonitrile gave β-cyano-ethylmethylamine **36**. Condensation of **36** with acetone cyanohydrin gave the dinitrile **37**, which in turn could be cyclized to enaminonitrile **38** as indicated in Scheme 14. Hydrolysis of **38** with HCl gave 1,2,2-trimethyl-3-pyrrolidinone **39** [16].

Scheme 14



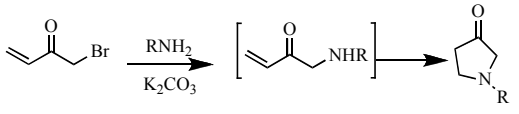
Treatment of diphenyl cyclopropenone with imines gave 1-methyl-2,3-diphenyl-2-pyrrolin-4-ones **40** (R1 = Me, Ph, *p*-tolyl), which under $LiAlH_4$ reduction gave **41** (R = Me, Ph) (Scheme15) [17].

Scheme 15



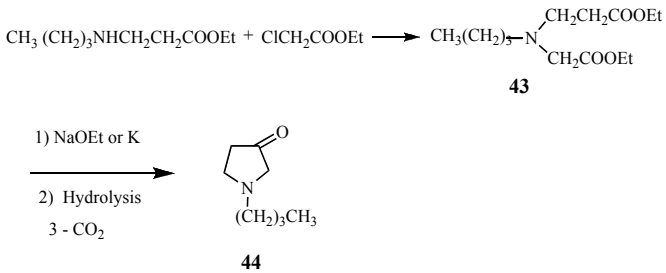
1-Bromobut-3-en-2-one reacted with a primary amine in the presence of potassium carbonate to afford 3-pyrrolidines **42** (R = Bn; *t*-Bu) through an intramolecular Michael reaction (Scheme16) [18].

Scheme 16



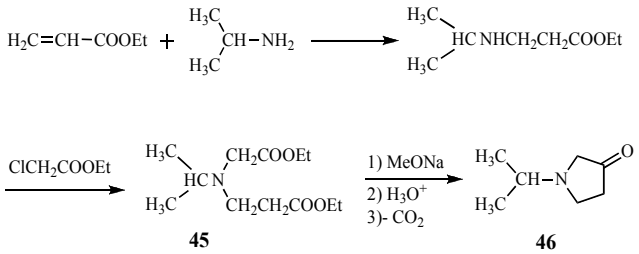
Condensation of ethyl chloroacetate with ethyl β-butylaminopropionate gave the diester **43**. Ring closure of **43** with sodium ethoxide or potassium metal followed by hydrolysis and decarboxylation gave 1-butyl-3-pyrrolidinone **44** (Scheme17) [8].

Scheme 17



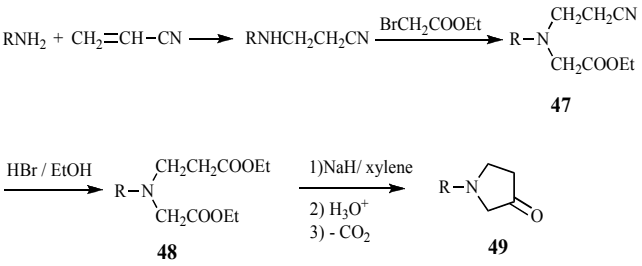
Adding isopropylamine to ethyl acrylate gave β-carbethoxyethyl-isopropylamine, which was alkylated with ethyl chloroacetate to the diester **45**. Cyclization of **45** in sodium methoxide followed by acid hydrolysis and decarboxylation gave 1-isopropyl-3-pyrrolidinone **46** (Scheme18) [19].

Scheme 18



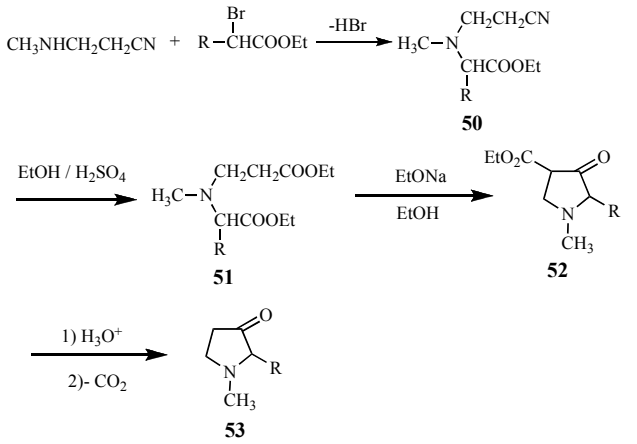
Adding primary amines to acrylonitrile gave β-cyano alkyl ethyl amines. Alkylation of the latter with ethyl bromoacetate gave the cyano esters **47**. Hydrolysis of **47** with HBr/EtOH afforded the diesters **48**. Cyclization of **48** with sodium hydride in xylene followed by acid hydrolysis and decarboxylation gave *N*-alkyl-3-pyrrolidinones (R = benzyl, phenylethyl, 2-benzoylethyl) **49** (Scheme19) [20,21].

Scheme 19



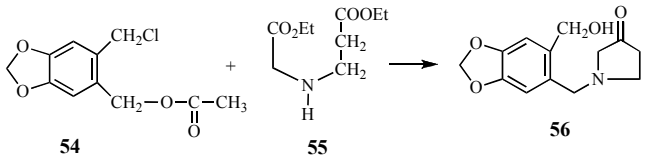
Adding α-bromoester to β-cyanoethylmethylamine gave the cyano esters **50**. Acid hydrolysis of **50** with $EtOH/H_2SO_4$ gave the diesters **51**. Cyclization of **51** in ethanolic sodium ethoxide afforded the keto ester **52**. Acid hydrolysis followed by decarboxylation of **52** gave 3-pyrrolidinones (R = H, Me) **53** (Scheme 20) [22].

Scheme 20



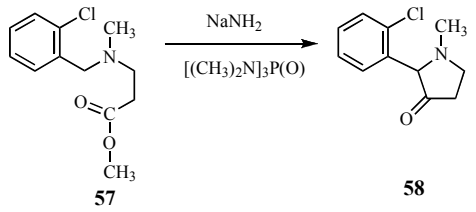
Condensation of chloro ester **54** with diester **55** followed by subsequent Dieckmann cyclization and decarboxylation gave the 3-pyrrolidinone derivative **56** (Scheme 21) [23].

Scheme 21



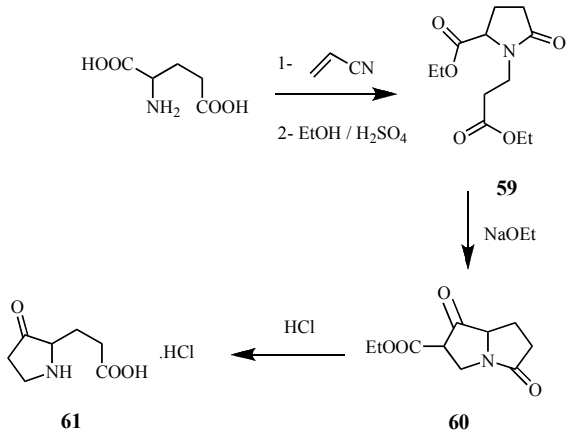
Treatment of methyl ester **57** with sodium amide and hexamethylphosphoramide gave 1-methyl-2-(*o*-chlorophenyl)-3-pyrrolidinone **58** (Scheme 22)[24].

Scheme 22



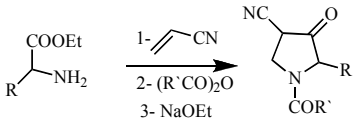
Ethyl *N*-(β-carbethoxyethyl)-5-oxo-2-pyrrolidinecarboxylate **59** prepared from L-(+)-glutamic acid and acrylonitrile which was hydrolyzed and esterified in absolute ethanol containing concentrated sulfuric acid. Cyclization of **59** with sodium ethoxide produced ethyl 1,5-dioxopyrrolizidine-2-carboxylate **60**. Decarboxylation of the pyrrolizidine **60** in hot hydrochloric acid was accompanied by lactam ring hydrolysis, so that the product was the 3-oxopyrrolidine acid **61** (Scheme 23) [25].

Scheme 23



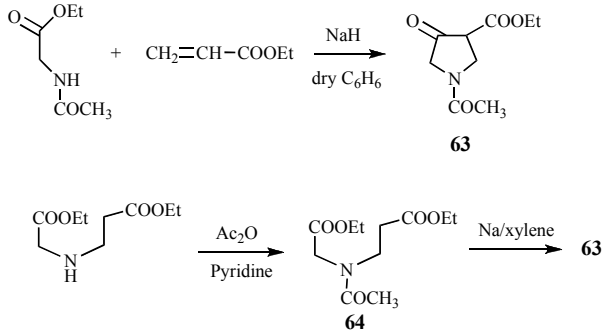
Successive cyanoethylation and acylation of the amino group, followed by Dieckmann cyclization yielded 2-substituted 1-acyl-4-cyano-3-oxopyrrolidines **62** (R = H, Me, benzyl; R` = Me, Ph) (Scheme 24) [26].

Scheme 24



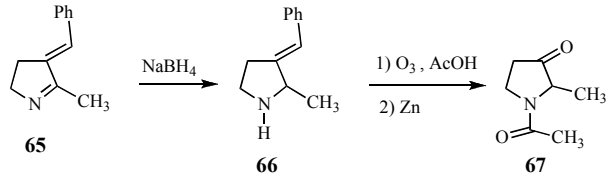
Condensation of *N*-acetyl ethyl glycinate with ethyl acrylate in pure sodium hydride and dry benzene gave *N*-acetyl-4-carbethoxy-3-pyrrolidinone **63**. On the other hand, heating of ethyl β-carbethoxymethyl aminopropionate in pyridine and acetic anhydride gave the acetyl diester **64**, which cyclized in Na/xylene to give **63** (Scheme 25) [27].

Scheme 25



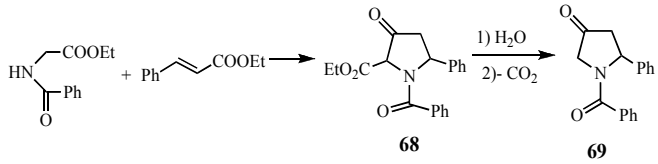
Reduction of 2-methyl-3-benzylidene-1-pyrroline **65** with $NaBH_4$ gave 2-methyl-3-benzylidenepyrrolidine **66**. Ozonolysis of **66** in acetic acid and decomposing of the resulting ozonide with zinc dust gave 1-acetyl-2-methyl-3-pyrrolidinone **67** (Scheme 26) [28].

Scheme 26



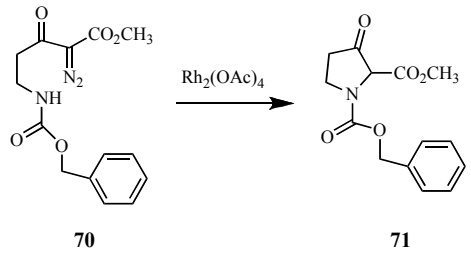
Michael condensation of ethyl hippurate with ethyl cinnamate gave the keto ester **68**, hydrolysis and decarboxylation of **68** gave 1-benzoyl-2-phenyl-4-pyrrolidinone **69** (Scheme 27) [29]

Scheme 27



1-(Benzyloxycarbonyl)-2-(methoxycarbonyl)-3-oxopyrrolidine **71** was prepared by addition of $Rh_2(OAc)_4$ to a solution of the α-diazo β-keto ester **70** (Scheme 28) [30].

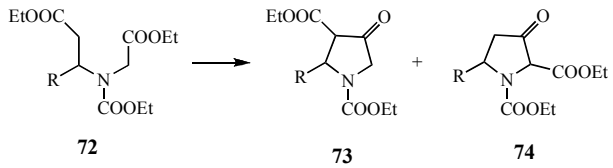
Scheme 28



1.4. *N*-Carbethoxy-3-pyrrolidinones

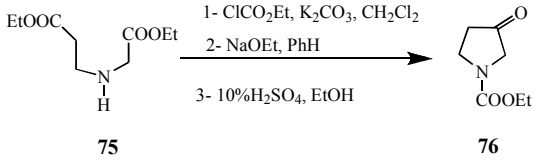
Ethyl *N*-ethoxycarbonyl-S-(2-ethoxycarbony1ethyl)-glycinate **72** (R = H, CH_3, COOEt, C_6H_5) under non-equilibrating conditions, both ethyl l-ethoxycarbonyl-4-oxopyrrolidine-3-carboxylate **73** and ethyl l-ethoxy-carbonyl-3-oxopyrrolidine-2-carboxylate **74** have been obtained in roughly equal yield (Scheme 29) [31].

Scheme 29



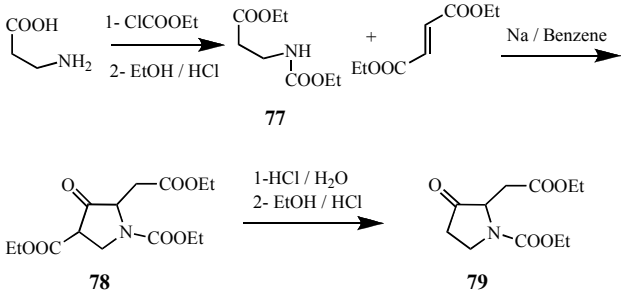
Ethyl 3-oxopyrrolidine-1-carboxylate **76** was prepared from ethyl 3-(ethoxycarbonyl)methylamino)propanoate **75** by reaction firstly with ethyl chloroformate and potassium carbonate in dichloromethane followed by intramolecular Dieckmann condensation in sodium ethoxide and benzene and finally hydrolysis of the ester group (Scheme 30) [32,33].

Scheme 30



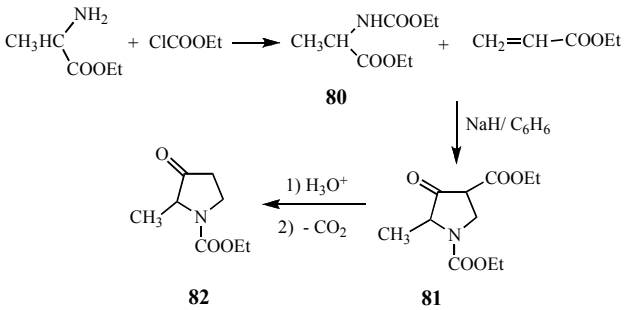
β-Alanine reacted with ethyl chloroformate in sodium hydroxide and then esterified to give ethyl *N*-ethoxy-carbonyl-β-aminopropionate **77**. Reaction of **77** with diethyl fumarate afforded **78**, which cyclized in benzene and sodium and then hydrolyzed to afford ethyl 2-(ethoxycarbonyl)methyl)-3-oxopyrrolidine-1-carboxylate **79** (Scheme 31) [34].

Scheme 31



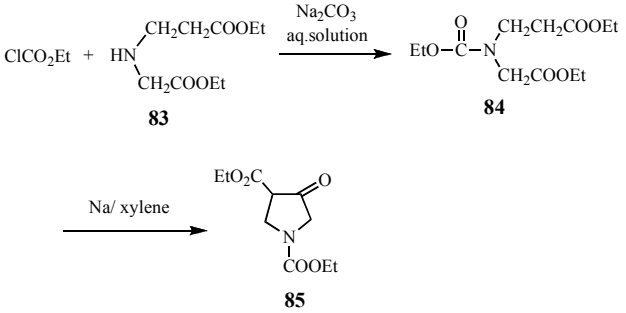
Condensation of DL-α-alanine ethyl ester and ethyl chloroformate gave the diester **80**. Addition of **80** to ethyl acrylate in sodium hydride and benzene gave the keto diester **81**. Acid hydrolysis and decarboxylation of **81** gave 1-carbethoxy-2-methyl-3-pyrrolidinone **82** (Scheme 32) [35].

Scheme 32



Heating of ethyl chloroformate with the diester **83** in aqueous solution of sodium carbonate gave the triester **84**. Cyclization of **84** in Na/xylene gave diethyl 4-oxo-pyrrolidin-1,3-dicarboxylate **85** (Scheme 33) [36].

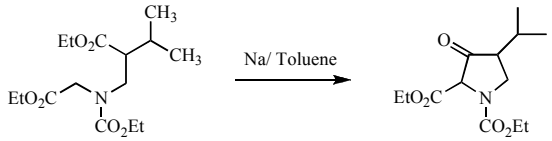
Scheme 33



83 **84** **85**

1,2-Dicarbethoxy-4-isopropyl-3-pyrrolidinone **87** was prepared from the cyclization of the triester **86** in Na/toluene (Scheme 34) [37].

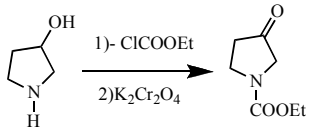
Scheme 34



86 **87**

Ethyl 3-oxopyrrolidine-1-carboxylate **89** was prepared from pyrrolidin-3-ol **88** by reaction with ethyl chloroformate followed by oxidation with potassium chromate (Scheme 35) [38].

Scheme 35

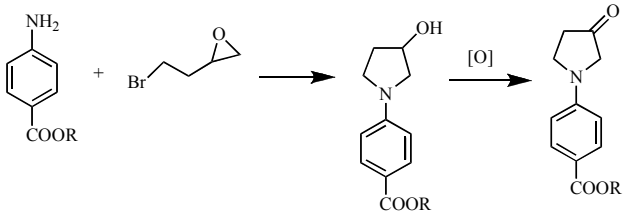


88 **89**

1.5. N-Aryl-3-pyrrolidinones

The condensation of 4-bromo-1,2-epoxybutane with a slight excess of an alkyl 4-aminobenzoate under argon in a sealed reaction flask at 120 °C for 2-4 h afforded *N*-[4'-(alkoxycarbonyl)-phenyl]-3-pyrrolidinol **90** which will undergo Moffatt oxidation (with either trifluoroacetic acid or 99% phosphoric acid as the acid catalyst) to give 3-pyrrolidinone **91** (R = Me, Et, *t*-Bu) (Scheme 36) [39].

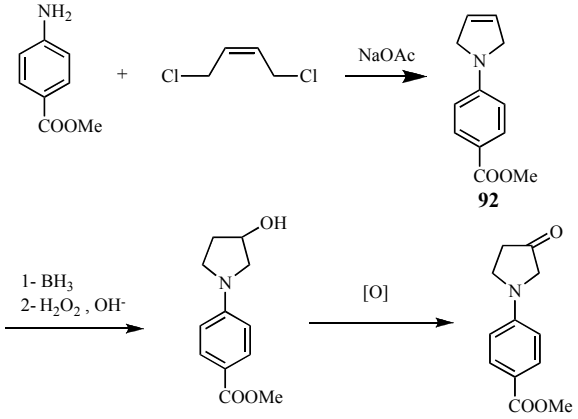
Scheme 36



90 **91**

Alkylation of methyl 4-aminobenzoate with *cis*-1,4-dichloro-2-butene in methanol containing sodium acetate and a catalytic amount of potassium iodide (Finkelstein conditions) gave an excellent yield of the 3-pyrroline **92**. Hydroboration-oxidation of **92** afforded 3-pyrrolidinol **93** which underwent oxidation to the 3-pyrrolidinone **94** (Scheme 37) [39].

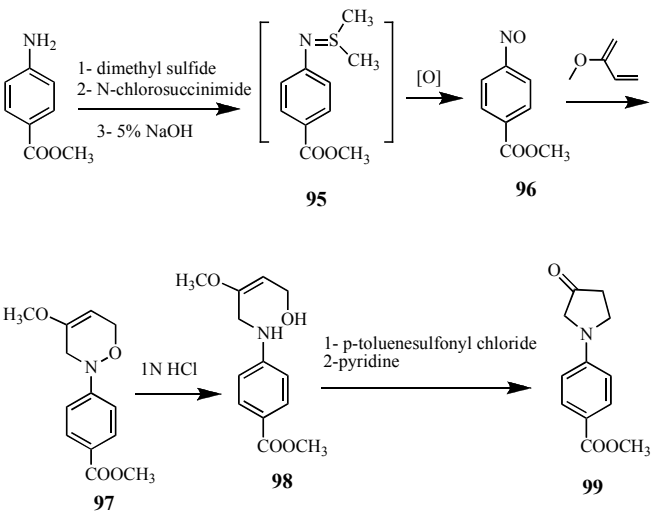
Scheme 37



92 **93** **94**

Treatment of methyl *p*-aminobenzoate with dimethyl sulfide, followed immediately by the addition of *N*-chlorosuccinimide in dichloromethane at -25 °C, gave sulfilimine **95**. Oxidation of **95** *in situ* at 0°C to methyl *p*-nitrosobenzoate **96** was accomplished by addition of 1.2 equiv of *m*-chloroperbenzoic acid. Diels-Alder reaction of **96** with 2-methoxy-1,3-butadiene at 0°C led to dihydro-2*H*-1,2-oxazine **97**. Hydrolysis of **97** by 1 *N* hydrochloric acid at room temperature afforded the tetrahydro-2*H*-1,2-oxazinone **98**, hydrogenation of **98** over Pd/C led to the amino alcohol which on dehydrative ring closure gave 3-pyrrolidinone **99** (Scheme 38) [40].

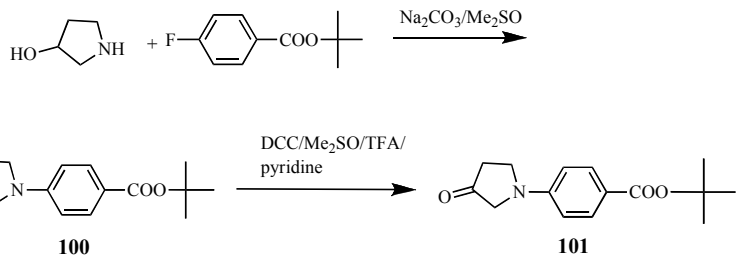
Scheme 38



95 **96** **97** **98** **99**

Pyrrolidin-3-ol reacted with *t*-butyl 4-fluorobenzoate in DMSO in the presence of sodium carbonate to give 3-pyrrolidinol **100** which was oxidized to 3-pyrrolidinone **101** (Scheme 39) [41].

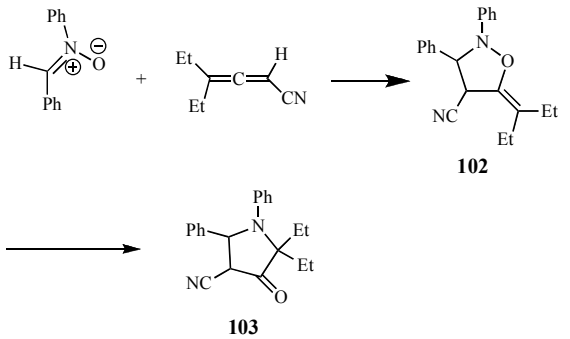
Scheme 39



100 **101**

Dipolar cycloaddition of nitrones with electron-deficient allenes gives 5-exo-ethylene substituted isoxazolidines **102**. Smooth rearrangement of **102** produced 3-pyrrolidinones **103** (Scheme 40) [42].

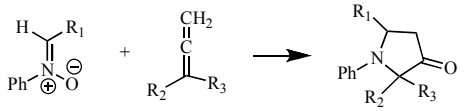
Scheme 40



102 **103**

An intermolecular cycloaddition of C,N-diphenyl-nitrone with allene afforded 3-pyrrolidinone **104** (R_1=COPh, R_2=R_3 =H or R_1= Ph, R_2=R_3= Me) (Scheme 41) [43].

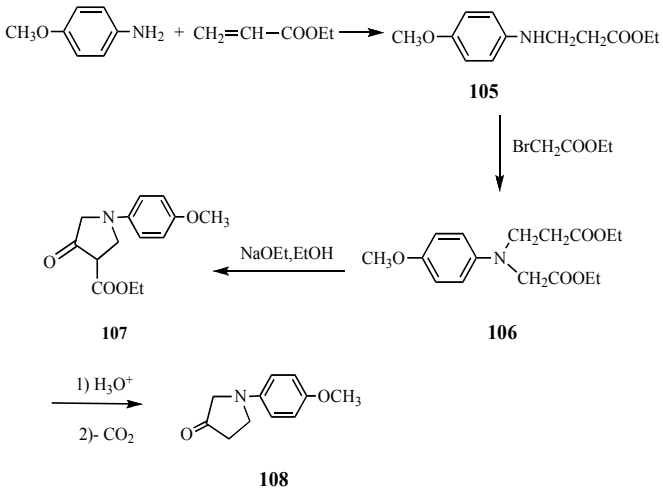
Scheme 41



104

Condensation of *p*-anisidine and ethyl acrylate gave ethyl *N*-(4`-methoxyphenyl)-β-aminopropionate **105**, which alkylated with ethyl bromoacetate to give the diester **106**, compound **106** was subsequently converted into **107** by intramolecular cyclization with base. Acid hydrolysis of the keto ester **107** followed by decarboxyaltion gave 1-(4'-methoxyphenyl)-3-pyrrolidinone **108** (Scheme 42) [44,45].

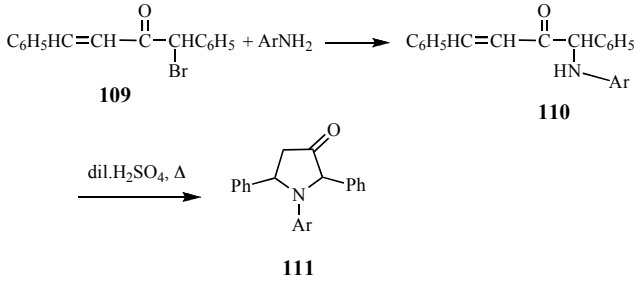
Scheme 42



105 **106** **107** **108**

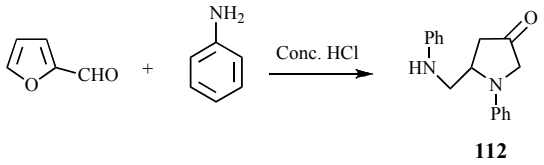
Reaction of α,β-unsaturated bromoketone **109** with primary arylamines gave 1-arylamino-1,4-diphenyl-3-buten-2-ones **110**, which cyclized to 1-aryl-2,5-diphenyl-3-pyrrolidinones **111** (Ar = C_6H_5,4-Cl-C_6H_4 and 4-OCH_3-C_6H_4) by heating with diluted sulfuric acid (Scheme 43) [46,47].

Scheme 43



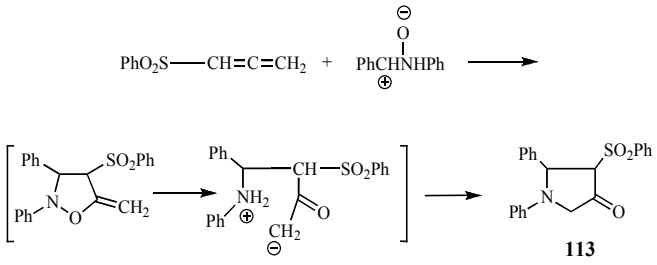
Reaction of furfural with aniline in presence of conc. HCl gave 5-phenylaminomethyl-1-phenyl-3-pyrrolidinone **112** (Scheme 44) [48].

Scheme 44



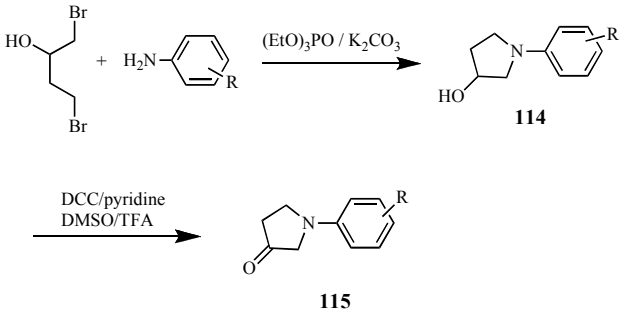
1,3-Dipolar cycloaddition of (phenylsulfonyl)-propadiene with a nitrone in chloroform solution at room temperature gave 3-pyrrolidinone derivative **113** Scheme 45) [49].

Scheme 45



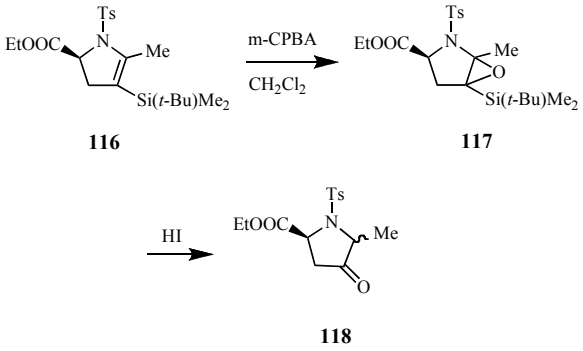
1-(4-Alkyloxycarbonyl-phenyl)-3-pyrrolidinones **115** (R = H, 3-Me, 4-CN, 4-NO_2, 2-F, 4-F, *etc*) were prepared by condensation of 1,4-dibromo-2-butanol with alkyl-*p*-aminobenzoate, followed by oxidation of 1-(4-alkyloxy-carbonyl-phenyl)-3-pyrrolidinols **114** by (DCC/pyridine/DMSO/TFA) (Scheme 46) [50].

Scheme 46



The vinylsilane functionality in pyrroline **116** can be epoxidized with *m*-CPBA to produce epoxypyrrolidine **117**. Subsequent treatment with aqueous HI solution at room temperature furnished desilylated 3-pyrrolidinone **118** (Scheme 47) [51].

Scheme 47



1.6. 3-Oxopyrrolidin-1-oxide

5,5-Dimethyl-1-pyrroline-1-oxide was converted either by SeO_2 or $(CH_3)_2CHCH_2CH_2ONO$ into 3-oxo-1-pyrroline-1-oxide **119**, but the reaction is not general for other nitrones, three 3-carbethoxy-1-pyrroline-1-oxides **120** (R=Ph, Me_3C, H) were prepared by base-catalyzed acylation of simple pyrroline oxide, and nitrosation of **120** (R=Ph) resulted in the formation of 3-oxopyrrolidine **121** (Figure 1) [52].

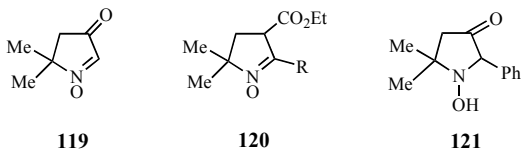
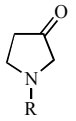


Figure 1

2. GENERAL CHARACTERISTICS

3-Pyrrolidinones **122** (R = CH_2Ph, CO_2Me, SO_2CF_3) were considered as α-amino ketones afforded enolates

away from nitrogen under kinetic base, thermodynamic base and thermodynamic acid conditions (Figure 2) [53].



122

Figure 2

Electron-impact mass spectra of 3-pyrrolidinones show that the mechanism of the fragmentation varies with the substituent on the nitrogen atom; when this substituent is alkyl, fragmentation proceeds by two pathways; loss of CO to give an azetidine intermediate before breaking down further, or elimination of an unsaturated aliphatic amine with the formation of a cyclopropanone. When the N-substituent is aryl, the pathway involves elimination of other substituents and CO, then reaction of the aryl group with the heterocycle radical ion gives methylindole or dihydroquinoline ion intermediates [54].

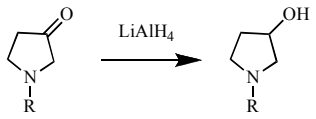
3. REACTIONS

3.1. Reduction

3.1.1 Reduction to 3-pyrrolidinols

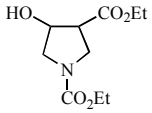
Reduction of 3-pyrrolidinones with lithium aluminium hydride or sodium bohydride afforded 3-pyrrolidinols **123** (R = alkyl; cycloalkyl and aryl) (Scheme 48) [18,39,55,56].

Scheme 48



123

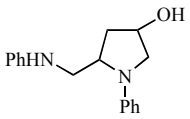
Diethyl 4-oxopyrrolidine-1,3-dicarboxylate was reduced over PtO_2 or Raney nickel as a catalyst to diethyl 4-hydroxypyrrolidine-1,3-dicarboxylate **124** (Figure 3)[36].



124

Figure 3

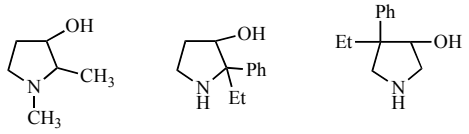
5-Phenylaminomethyl-1-phenyl-3-hydroxypyrrolidine **125** was obtained by reduction of compound **112** over Raney nickel (Figure 4)[48].



125

Figure 4

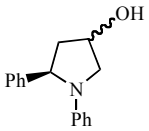
1,2-Dimethyl-3-pyrrolidinone **35**, 2-ethyl-2-phenyl-3-pyrrolidinone **7** and 4-ethyl-4-phenyl-3-pyrrolidinone **10** were reduced with $NaBH_4$ to 1,2-dimethyl-3-pyrrolidinol **126**, 2-ethyl-2-phenyl-3-pyrrolidinol **127** and 4-ethyl-4-phenyl-3-pyrrolidinol **128** (Figure 5)[3,15].



126 **127** **128**

Figure 5

1,5-Diphenyl-3-pyrrolidinone was reduced with $NaBH_4$ to a mixture of *cis*- and *trans*-1,5-diphenyl-3-hydroxy-pyrrolidine **129** (Figure 6) [57].

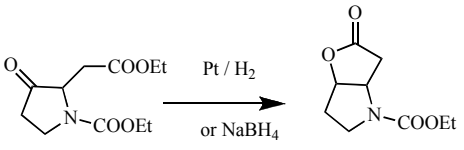


129

Figure 6

Ethyl tetrahydro-2-oxo-2*H*-furo[3,2-*b*]pyrrole-4(5*H*)-carboxylate **131** was prepared by reduction of ethyl 2-(ethoxycarbonyl)methyl)-3-oxopyrrolidine-1-carboxylate **130** with hydrogen and platinum or by sodium borohydride (Scheme 49) [34].

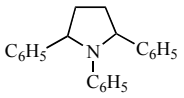
Scheme 49



130 **131**

3.1.2. Wolff-Kishner reduction

The Wolff-Kishner reduction of 1,2,5-triphenyl-3-pyrrolidinone gave a mixture of meso and racemic 1,2,5-triphenylpyrrolidine **132** (Figure 7)[30].

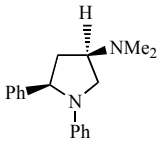


132

Figure 7

3.1.3. Reduction amination

cis-1,5-Diphenyl-3-dimethylaminopyrrolidine **133** was prepared from the corresponding 3-pyrrolidinone by conversion to oxime then to oxime acetate with acetic anhydride. Stereoselective reduction of oxime acetate with boron hydride led to the *cis*-amine, which was converted to the trimethylammonium derivative with methyl iodide, then reduced with $LiAlH_4$ (Figure 8)[57,58].



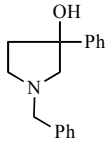
133

Figure 8

3.2. With organometallic reagents

3.2.1. Grignard reaction

1-Benzyl-3-phenyl-3-pyrrolidinol **134** was prepared by the action of PhMgBr on 1-benzyl-3-pyrrolidinone (Figure 9) [19].



134

Figure 9

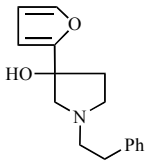
In a similar manner, 1-butyl-3-phenyl; 1-methyl-3-(4'-methoxphenyl); 1-isobutyl-3-(4'-methoxyphenyl) and 1-benzyl-3-(4'-methoxyphenyl) 3-pyrrolidinols were prepared [25].

Similarly, 1-acetyl-3-phenyl-3-pyrrolidinol **135** and 1-carbethoxy-3-substituted-3-pyrrolidinols **136** (R = phenyl; *p*-chlorophenyl; *p*-methoxyphenyl; *p*-benzylphenyl; 2-thienyl and 3,5-diphenyl) were prepared (Figure 10) [19,20].

135 **136**

Figure 10

3-(2'-Furyl)-1-phenylethyl-3-pyrrolidinol **137** was prepared by reaction of 3-pyrrolidinone with 2-furyl magnesium bromide (Figure 11) [26].

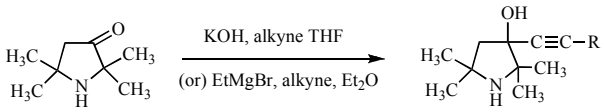


137

Figure 11

3-Alkynyl-3-pyrrolidinols **138** (R = H and Ph) have been prepared by alkylation of 3-pyrrolidinone derivatives by Favorskii ethylation or the Grignard Lotsitch method (Scheme 50) [69].

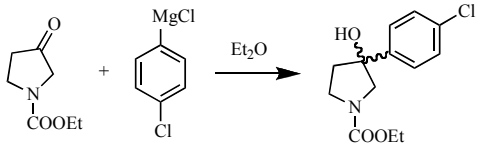
Scheme 50



138

Ethyl 3-oxopyrrolidine-1-carboxylate reacted with 4-chlorophenylmagnesium chloride in dry ether to afford the *tert*-alcohol **139** (Scheme 51) [38].

Scheme 51

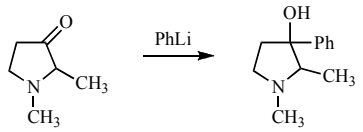


139

3.2.2. With organolithium compounds

Reaction of 1,2-dimethyl-3-pyrrolidinone **35** with PhLi gave 1,2-dimethyl-3-phenyl-3-pyrrolidinol **140** (Scheme 52) [60].

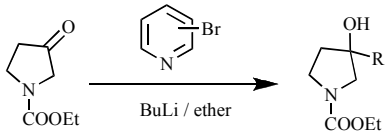
Scheme 52



35 **140**

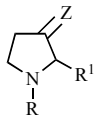
Reaction of 2-, 3- or 4-bromopyridine with *n*-butyllithium in dry ether at -78°C and reaction of the resuling pyridyl-lithiums with 1-carboethoxy-3-pyrrolidinone gave isomeric ethyl 3-(2-, 3-, or 4-pyridyl)-3-hydroxypyrrolidine-1-carboxylates **141** (Scheme 53) [47,61].

Scheme 53



141

3-Substituted-3-hydroxypyrrolidines (R,R_1 = Me, Et; Z = OH, $CHPh_2$; OH, 10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-yl, CPh_2, 10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-ylidene; 5,6,7,12-tetrahydrodibenzo[*a*,*d*]cyclooctene-12-ylidene) **142** were prepared by reaction of 3-pyrrolidinones with a suitable hydrocarbon in the presence of BuLi followed by optional dehydration (Figure 12) [46].

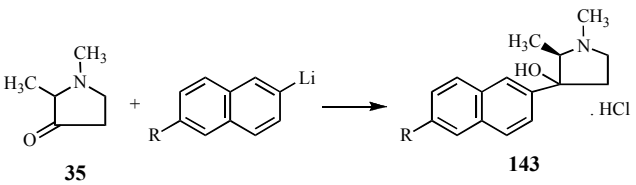


142

Figure 12

Lithiation of 2-bromo-6-substituted naphthalene followed by stereoselective addition to 3-pyrrolidinone derivative **35** gave a racemic mixture of 3-naphthyl-3-hydroxypyrrolidine hydrochloride **143** (R = H, F, OCH_3) (Scheme 54) [48].

Scheme 54

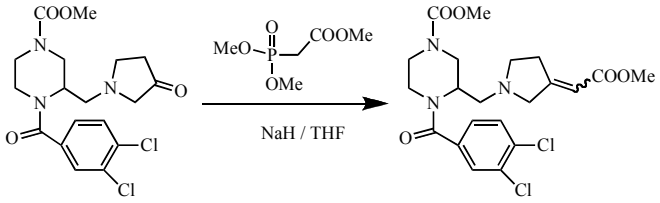


35 **143**

3.2.3. With Organophosphorus reagents

3-Pyrrolidinone reacted with trimethyl phosphonoacetate in the presence of sodium hydride to give (*Z* or *E)* methyl 4-[(3,4-dichlorophenyl)acetyl]-3-[[3-(2-methoxy-2-oxoethylidene)-l-pyrrolidinyl]methyl]-l-piperazinecarboxylate **144** (Scheme 55) [62].

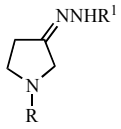
Scheme 55



144

3.3. With hydrazines and hydrazides

N-Alkyl-3-pyrrolidinylhydrazones **145** (R = Me, iso-Pr, Bu, Et, Me; R1 = iso-Pr, Ac) were prepared by reaction of *N*-alkyl-3-pyrrolidinones with hydrazines (Figure 13)[16].

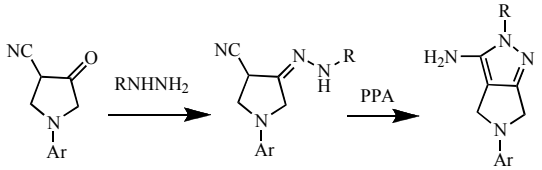


145

Figure 13

3-Pyrrolidinones (Ar = 4-Me-C_6H_4, 4-Me-OC_6H_4) reacted with hydrazines (R = H, Ph) to afford amino pyrrolopyrazoles **147** *via* hydrazones **146** by heating in polyphosphoric acid (Scheme 56) [63].

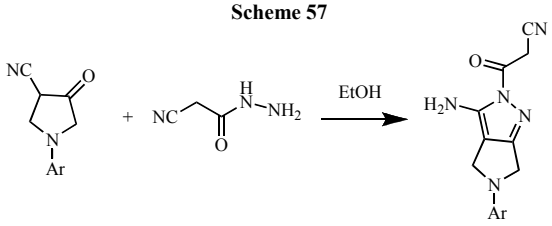
Scheme 56



146 **147**

3-Pyrrolidinones (Ar = 4-Me-C_6H_4, 4-MeO-C_6H_4) reacted with 2-cyanoacetohydrazide to give amino pyrrolopyrazole **148** (Scheme 57) [63].

Scheme 57

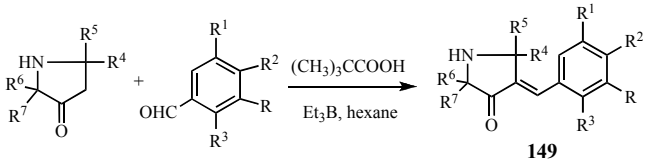


148

3.4. With aldehydes

Condensation of 3-pyrrolidinone derivatives with substituted benzaldehyde in trimethylacetic acid (pivalic acid), triethylborane and hexane gave 4-benzylidine-3-pyrrolidinone derivatives **149** (R, R_1 = H, OH, alkyl, alkoxy; R=R_1≠H; R_2, R_3=H, OH; R_4-R_7 = alkyl, aryl, (subs.) aralkyl) (Scheme 58) [64].

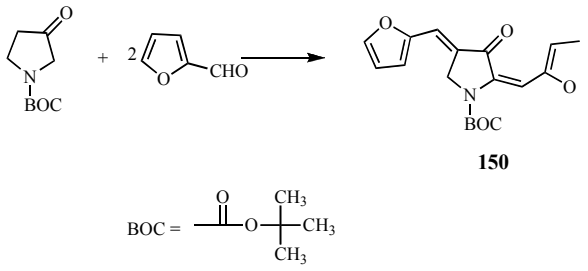
Scheme 58



149

N-protected 2,4-bis[(2-furyl)methylidene]pyrrolidine-3-one **150** was prepared by reaction of N-protected-3-pyrrolidinone with furan-2-carboxaldehyde (Scheme 59) [65].

Scheme 59

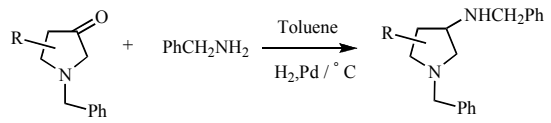


150

3.5. Condensation with amines

1-Benzyl-3-benzylaminopyrrolidines **151** (R= H and alkyl) were obtained from condensation of 3-pyrrolidinone derivatives with benzyl amine in toluene followed by hydrogenation (Scheme 60) [66].

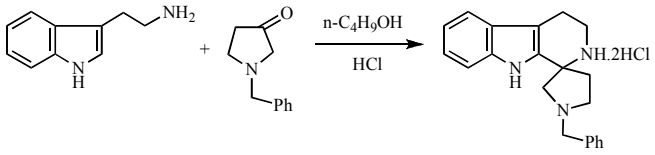
Scheme 60



151

Spiro[*N*-benzylpyrrolidin-3',1-(1,2,3,4-tetrahydro-β-carboline)]dihydrochloride **152** was prepared by the classical Pictet-Spengler reaction of tryptamine with *N*-benzyl-3-pyrrolidinone in *n*-butanol/HCl (Scheme 61) [29].

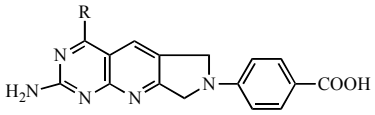
Scheme 61



152

3.6. Condensation with diamines

The 5-deazapteroic acid analogues **153** and **154** have been prepared by several different strategies starting from 1-[4'-(*tert*-butoxycarbonyl)phenyl]-3-pyrrolidinone **99** (Figure 14) [36].



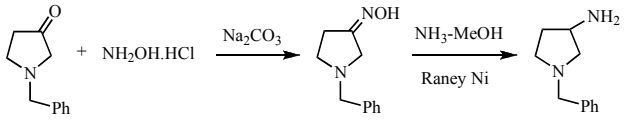
153, R= NH_2
154, R= OH

Figure 14

3.7. Reaction with hydroxylamine

1-Benzyl-3-pyrrolidinone reacts with $NH_2OH.HCl$ in the presence of Na_2CO_3 to give the corresponding oxime **155**. The hydrogenation of **155** in NH_3-MeOH over Raney nickel gave 3-amino-1-benzyl pyrrolidine **156** (Scheme 62) [37,67,68].

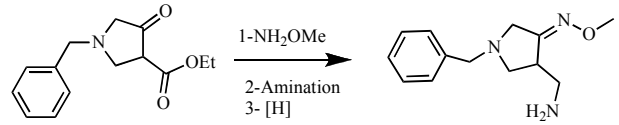
Scheme 62



155 **156**

3-Methoxyimino-4-aminomethylpyrrolidine derivative **157** was prepared from ethyl 1-benzyl-4-oxopyrrolidine-3-carboxylate by reaction with methoxyamine compound followed by reductive amination (Scheme 63) [69].

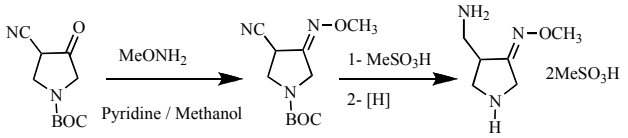
Scheme 63



157

4-Aminomethyl-3-methoxyiminopyrrolidinemethane sulfonate **159** was prepared from N-protected 4-cyano-3-oxopyrrolidine by reaction with methoxyamine hydrochloride to afford *N*-BOC-4-cyano-3-methoxyiminopyrrolidine **158** which reacted with methanesulfonic acid followed by reduction (Scheme 64) [70].

Scheme 64

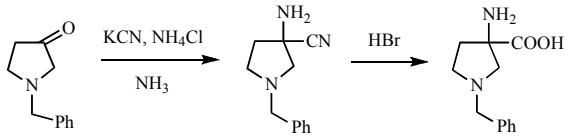


158 **159**

3.8. Reaction with ammonium salts

Treatment of 1-benzyl-3-pyrrolidinone with KCN and NH_4Cl in 28% aqueous ammonia gave (±)-3-amino-1-benzyl-3-cyanopyrrolidine **160**, subsequent hydrolysis of **160** with 48% HBr gave (±)-1-benzyl curcurbitine **161** (Scheme 65) [71].

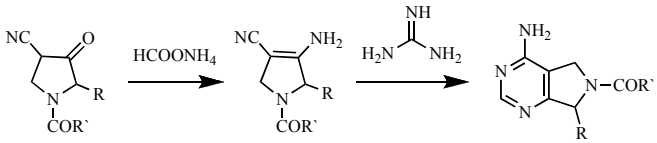
Scheme 65



160 **161**

Treatment of l-acyl-4-cyano-3-oxopyrrolidines (R = H, Me, benzyl; R' = Me, Ph) with ammonium formate afforded 2-substituted l-acyl-3-amino-4-cyano-3-pyrrolines **162**; Condensation of **162** with guanidine yielded 7-substituted 6-acyl-2,4-diamino-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidines **163** (Scheme 66) [26,45].

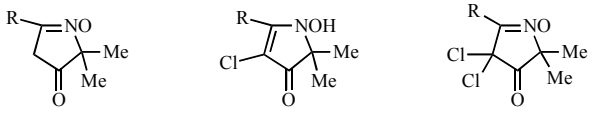
Scheme 66



162 **163**

3.9. Reaction with *N*-chlorosuccinimide

Reaction of β-oxonitrones with electrophilic reagents takes place either at the oxygen atom of the nitrone group or at the carbon atom between the carbonyl and nitrone group. Thus, treating **164** (R= Me) with *N*-chlorosuccinimide in carbon tetrachloride gave chloro derivative **165** as the major product, and with excess reagent gave the dichloro derivative **166** as the main product (Figure 15) [72].



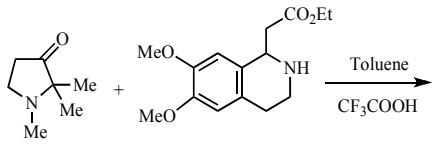
164 **165** **166**

Figure 15

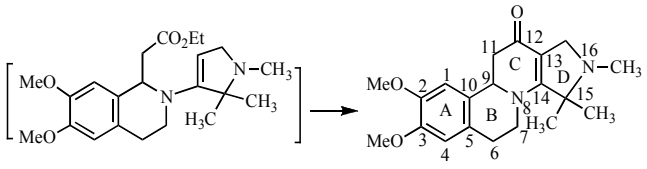
3.10. Reaction with isoquinoline derivatives

Reaction of 1-carbethoxymethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline with **39** in toluene and in the presence of a catalytic amount of trifluoroacetic acid gave 8,16-diaza-2,3-dimethoxy-15,15,16-trimethylgona-1,3,5(10),13-tetraen-12-one **167** (Scheme 67) [16].

Scheme 67



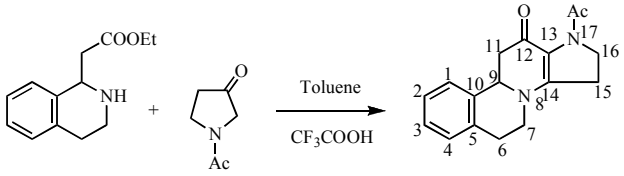
39



167

8,17-Diaza-17-acetylgona-1,3,5(10),13-tetraen-12-one **168** was synthesized from *N*-acetyl-3-pyrrolidinone and 1-carbethoxymethyl-1,2,3,4-tetrahydro-isoquinoline in toluene and with trifluoroacetic acid as a catalyst (Scheme 68) [16].

Scheme 68

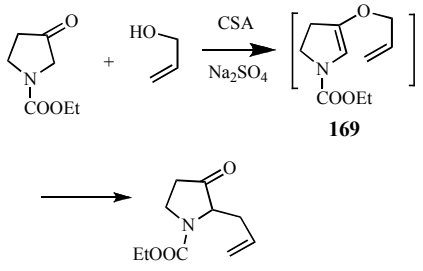


168

3.11. With allyl alcohols

Reaction of 3-pyrrolidinone in xylene with allyl alcohol in the presence of a catalytic amount of camphorsulfonic acid (CSA) and anhydrous sodium sulfate afforded ethyl 2-allyl-3-oxopyrrolidine-1-carboxylate **170** through an allyl enol ether intermediate **169** (Scheme 69) [32].

Scheme 69



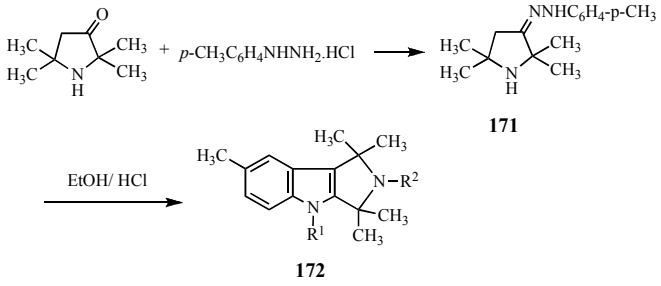
169

170

3.12. Fischer indole synthesis

Polymethyl 1,2,3,4-tetrahydropyrrolo[3,4-*b*]indole **172** was prepared by reaction of 2,2,5,5-tetramethyl-3-pyrrolidinone with arylhydrazine.HCl to give the corresponding hydrazone **171** which on treatment with EtOH/HCl afforded **172** (Scheme 70) [73].

Scheme 70

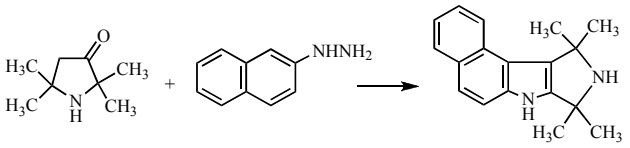


171

172

In a similar manner, **173** was prepared by reaction of β-naphthylhydrazine with the corresponding 3-pyrrolidinone (Scheme 71) [73].

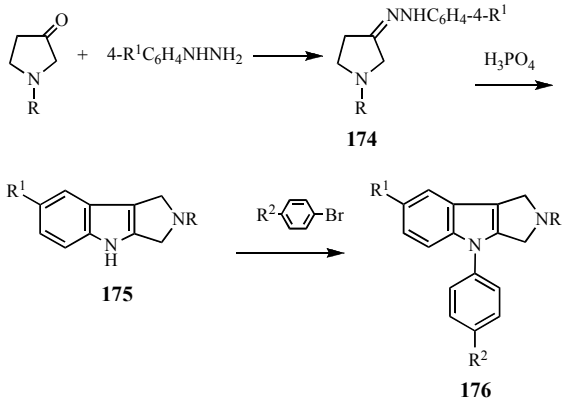
Scheme 71



173

1,2,3,4-Tetrahydropyrrolo[3,4-*b*]indoles **176** were prepared by condensation of 3-pyrrolidinone with *p*-substituted phenylhydrazine to give the corresponding hyrazones **174**, treatment of **174** with H_3PO_4 gave indole derivatives **175**, which on treatment with arylbromide afforded **176** (R= CH_3,CO_2Et; R_1= H, Br, Cl, F; R_2= H, OCH_3, F) (Scheme 72) [17].

Scheme 72



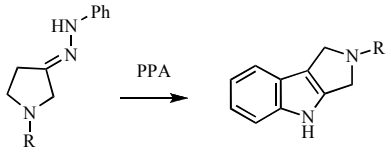
174

175

176

The Fischer cyclization of arylhydrazones of 3-pyrrolidinones afforded 1,2,3,4-tetrahydropyrrolo[3,4-*b*]indoles **177** (R = *n*-butyl, benzyl, and cyclohexyl) (Scheme 73) [74].

Scheme 73

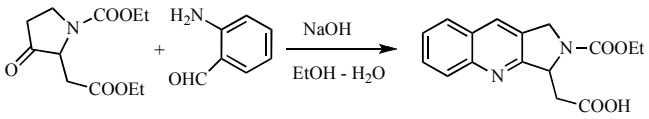


177

3.13. Friedlander condensation

A base-catalyzed Friedlander condensation of ethyl 2-(ethoxycarbonyl)methyl)-3-oxopyrrolidine-1-carboxylate with *o*-aminobenzaldehyde gave the tricyclic quinoline acid **178** (Scheme 74) [75-77].

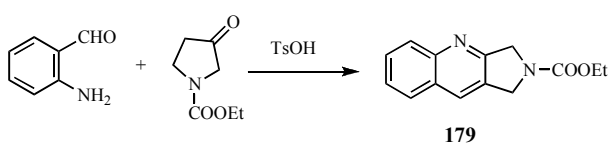
Scheme 74



178

Friedlander condensation of *o*-aminobenzaldehyde and *N*-carbethoxy-3-pyrrolidinone gave ethyl 1H-pyrrolo[3,4-*b*]quinoline-2(3*H*)-carboxylate **179** (Scheme 75) [78].

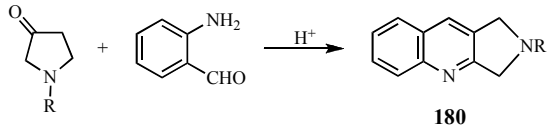
Scheme 75



179

2,3-Dihydro-1*H*-pyrrolo[3,4-*b*]quinolines **180** (R= $COCH_3$ and COOEt) are the key intermediate in the synthesis of camptothecin [pentacyclic alkaloid possessing anti-tumour activity], thus **180** was prepared by *p*-toluenesulphonic acid-catalyzed Friedlaender condensation of 3-pyrrolidinones with *o*-aminobenzaldehyde (Scheme 76) [49].

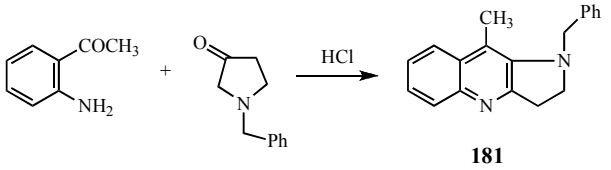
Scheme 76



180

The quinoline derivative **181** was prepared by cyclocondensation of 1-benzyl-3-pyrrolidinone and *o*-aminoacetophenone in 2 *N* HCl (Scheme 77) [79, 80].

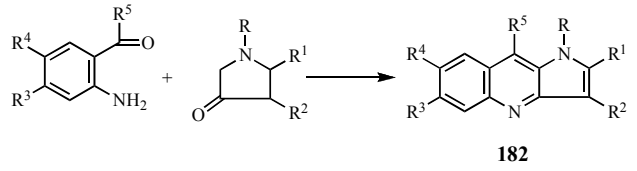
Scheme 77



181

1*H*-Pyrrolo[3,2-*b*]quinolines **182** (R= H, Ac, COOEt; R1= H, Me, Ph; R2=H, CHO, CO_2Et, CO_2CMe_3, Ac; R3= H, MeO; R_4= H, MeO, Cl; R_5= H, Ph.) were prepared by cyclocondensation of *o*-aminobenzaldehyde with 3-pyrrolidinone derivatives (Scheme 78) [39].

Scheme 78

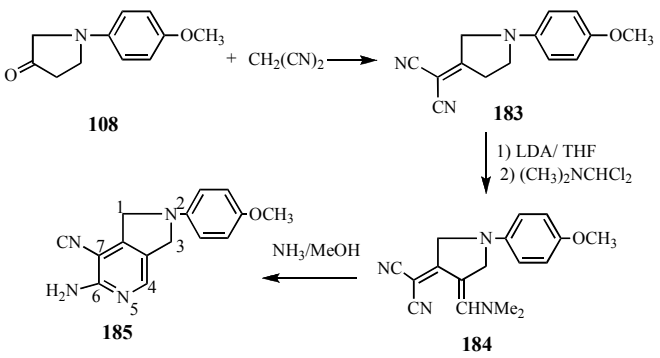


182

3.14. Knoevenagel reaction

Condensation of 1-(4'-methoxyphenyl)-3-pyrrolidinone **108** with malononitrile gave dicyanomethylene product **183** which readily polymerized. Lithiation of **183** with lithium diisopropylamide (LDA) in THF followed by treatment with (dimethylamino)methylenedichloride gave product **184**. Treating of **184** with NH_3/MeOH in a sealed container at 150°C gave 6-amino-7-cyano-2-(4'-methoxyphenyl)-2,3-dihydropyrrolo[3,4-*c*]pyridine **185** (Scheme 79) [44].

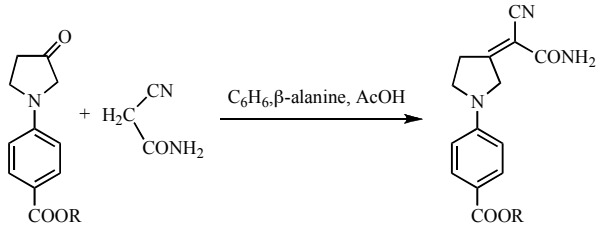
Scheme 79



108 **183** **185** **184**

Esters of 1-[4'-(carboxy)phenyl]-3-pyrrolidinones **91** were condensed with cyanoacetamide in benzene, β-alanine and acetic acid to give the Knoevenagl products **186** (R = Me, Et, t-Bu) (Scheme 80) [12,39].

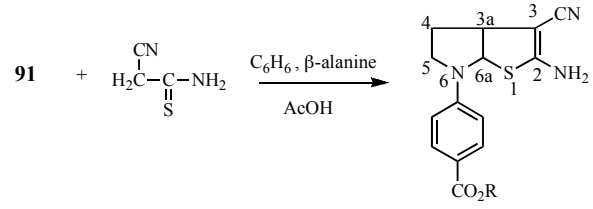
Scheme 80



91 **186**

Condensation of **91** with cyanothioacetamide under Knoevenagel conditions (reflux in benzene in the presence of β-alanine and acetic acid) did not give the anticipated Knoevenagel product analogous to **186**, but tetrahydrothieno[2,3-*b*]pyrrole **187** was obtained (Scheme 81) [10].

Scheme 81

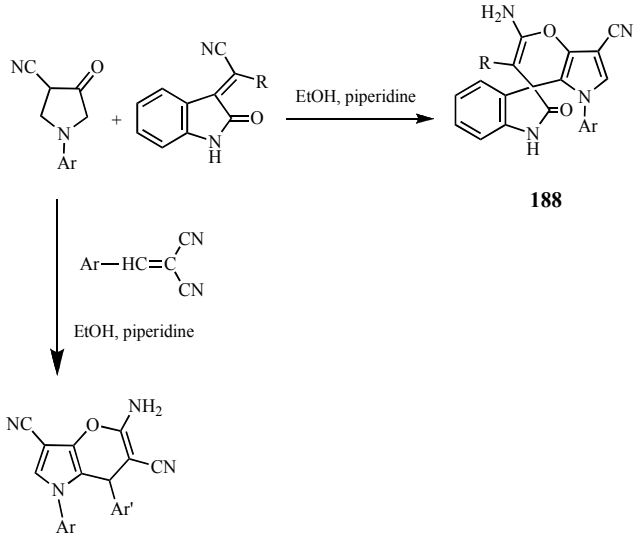


187

3.15. Michael Addition

Spiro-pyrrolo[3,2-*b*]-4-pyranyl-2-oxoindolines **188** and dicyanopyrrolo[3,2-*b*]-4-pyranes **189** were prepared from reaction of 3-pyrrolidinones with isatin-3-ylidiene (R = CN, COOEt) or arylidine malononitrile (Ar' = 4-Me-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4) in ethanol catalyzed by piperidine (Scheme 82) [81].

Scheme 82



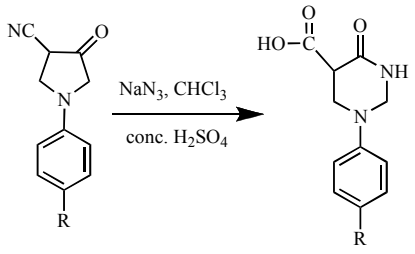
188

189

3.16. Schmidt rearrangement

3-Pyrrolidinones undergo Schmidt rearrangement conditions to afford hexahydropyrimidinones **190** (R = Me; OMe) (Scheme 83) [81].

Scheme 83

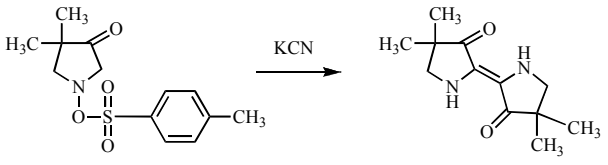


190

3.17. Dimerization

The indigo dye 4,4,4',4'-tetramethyl[2,2'-bipyrrolidinyl-idene]-3,3'-dione **191** was prepared by KCN dimerization of 4,4'-dimethyl-1-tosyl-3-pyrrolidinone (Scheme 84) [82].

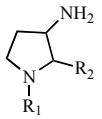
Scheme 84



191

4. MEDICINAL APPLICATIONS

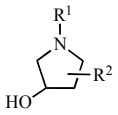
3-Pyrrolidinones used as a source of the D ring in the synthesis of diazasteroid groups such as 8,16- and 8,17-diazasteroid systems [16]. 3-Amino pyrrolidine **192** (R1 = Et, benzyl; R2 = H, Me) used as the starting material in preparation of drugs (Figure 16) [67].



192

Figure 16

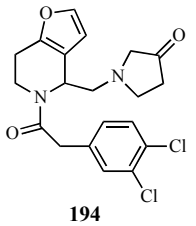
1-Substituted-3-hydroxypyrrolidines **193** (R1= C1-10 aliphatic hydrocarbonyl, aralkyl, aryl; R2= H and C1-4 alkyl) are useful as intermediate for drugs production (Figure 17)[83].



193

Figure 17

Pyrroloquinolines **178** can be used in biosynthesis of plant antitumor agents [76,78]. 4-[(Alkylamino)methyl]-furo[3,2-*c*]pyridine **194** is useful as selective K-Receptor Agonists (Figure 18) [84].

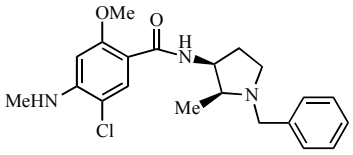


194

Figure 18

4-Substituted 1-(arylacetyl)-2-[(dialkylamino)methyl]-piperazine **144** used as a potent new class of K-receptor agonist [62].

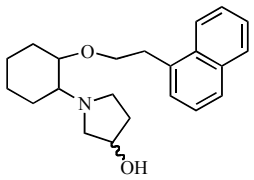
cis-*N*-(1-Benzyl-2-methylpyrrolidin-3-yl)-5-chloro-2-methoxy-4-(methylamino)benzamide (YM-09151-2) **195** demonstrates 13 times greater inhibitory effect on apomorphine-induced stereotyped behavior in rats than haloperidol (Figure 19)[67].



195

Figure 19

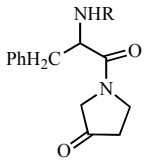
1-(2-(2-(Naphthalen-1-yl)ethoxy)cyclohexyl)pyrrolidin-3-ol **196** has been used as potential antiarrhythmic agent (Figure 20) [85].



196

Figure 20

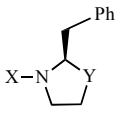
3-Pyrrolidinone **197** (R= nicotinyl, quinaldyl, PhCO, $(C_6H_5)_2NCO$, $(C_6H_5)N(CH_3CO)$, $CH_3(CH_2)_7OCO$ and $C_6H_5CH_2OCO$) acts as inhibitors of HIV-1 replication (Figure 21) [86].



197

Figure 21

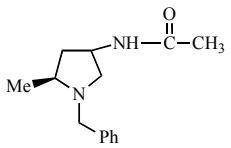
Compounds **198** (X = BOC-Protected L-amino acids Y = CHOH, C=O) are used as HIV protease inhibitors (Figure 22) [87,88].



198

Figure 22

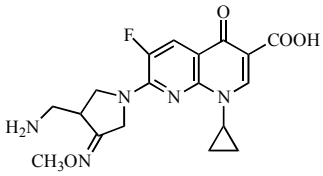
Chiral 4-amino-2-methylpyrrolidine derivatives **199** have been used as intermediates for quinolone carboxylate antibacterials (Figure 23) [89]



199

Figure 23

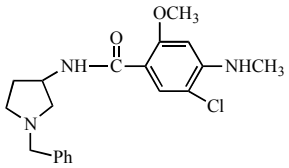
The fluoroquinolone containing oxime-substituted-(aminomethyl)pyrrolidine **200** acts as an antibacterial agent (Figure 24) [40,90-92].



200

Figure 24

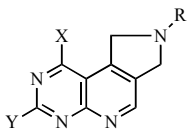
(±) Curcurbitine **161** has antihistaminic or antiallergic activity [71]. The benzamide **201** acts as nervous system depressants [93], quinoline derivative **181** is useful as appetite depressants [79], and pyrrolidinyl naphthalene **143** has antinociceptive activity (Figure 25) [48].



201

Figure 25

4-Benzylidene-3-pyrrolidinone **149** acts as sunscreens, antioxidants and skin antinflammatories [64]. 6,7-Dihydropyrrolo[3,4-*c*]pyrido[2,3-*d*]pyrimidine derivatives **202** (R = alkyl, (un)substituted aryl, (un)substituted alkyl aryl; X, Y = OH, NH_2, SH) used as potential anticancer agents (Figure 26) [94].

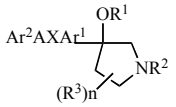


202

Figure 26

3-Substituted-3-hydroxypyrrolidines **142** have para-sympthomimetic activity [46]. 3-Hydroxy-3-(substituted alkyl)pyrrolidines **203** (Ar_1=(subs.)Ph or naphthyl; A=

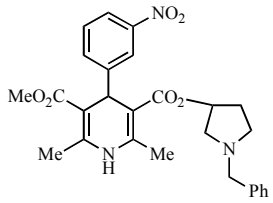
direct link to X, C1-4 alkyne; X= O, SO, SO_2; Ar_2= phenylene, pyridinyl, furanyl; R_1= C1-4 alkyl; R_2= C1-4 alkyl; R_3= H, HO; n= 1,2) act as 5-lipoxygenase inhibitors (Figure 27) [95].



203

Figure 27

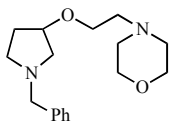
The dextrorotatory diastereoisomer **204** was useful as vasodilator [96] or useful as antihypertensive and antianginol [97]. *trans* and *cis*-1,5-Diphenyl-3-dimethyl-aminopyrrolidines **133** were useful as histamine H_1-receptor antagonists (Figure 28) [57].



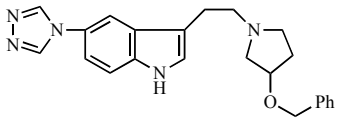
204

Figure 28

Morpholinoethoxypyrrolidine **205** acts as an antihypertensive agent [98]. The azolyl indole derivative **206** acts as 5-$HT_{1D\alpha}$ receptor agonists (Figure 29) [99].



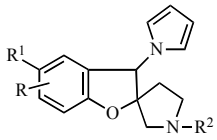
205



206

Figure 29

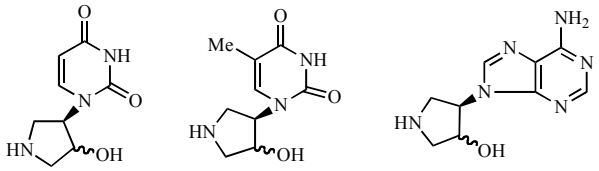
Spiro(dihydrobenzofuran)pyrrolidines **207** (R= H, alkyl; R1= H, halo; R_2= H, alkyl, alkoxycarbonyl) exhibit analgesic and antihypertensive activity (Figure 30) [100].



207

Figure 30

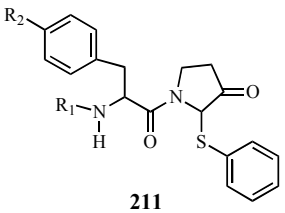
4-Pyrimidinyl and 4-purinylpyrrolidin-3-ol nucleoside analogues **208**, **209** and **210** exemplify a class of potential anticancer and antivirial agents (Figure 31) [101].



208 **209** **210**

Figure 31

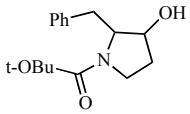
3-Pyrrolidinones **211** (R_1 = nicotinyl, 2-quinoleyl; R_2 = H, OH, OMe) are considered to be useful as inhibitors of HIV-1 replication (Figure 32) [102,103].



211

Figure 32

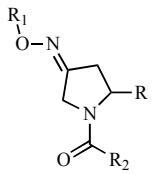
Pyrrolidin-3-ol derivative **212** used as HIV protease inhibitors (Figure 33) [104].



212

Figure 33

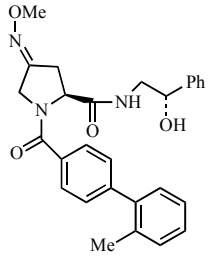
Pyrrolidine oximes **213** (R = (un)substituted 3- or 5-oxadiazolyl, a carbamoyl group; R1 = H, alkyl; R2 = aryl, heteroaryl, cycloalkyl, cycloalkenyl) are useful in treatment and/or prevention of preterm labor, premature birth and dysmenorrhea (Figure 34) [105].



213

Figure 34

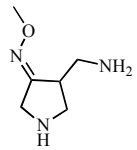
The pyrrolidine **214** is used as Bax inhibitors and oxytocin antagonists (Figure 35) [106-109].



214

Figure 35

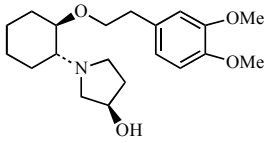
3-Aminomethyl-4-*Z*-methoxyiminopyrrolidine **215** is an intermediate in the production of the quinoline antibiotic gemifloxacin (Figure 36) [110].



215

Figure 36

(*R*)-1-((1*R*,2*R*)-2-(3,4-Dimethoxyphenethyloxy)cyclohexyl)pyrrolidin-3-ol **216** can be used for treatment of arrhythmia (Figure 37) [111].



216

Figure 37

REFERENCES

[1] Hong, C.Y.; Kim, Y.K.; Chang, J. H.; Kim, S. H.; Choi, H.; Nam, D. H.; Kim Y. Z.; Kwak, J. H. *J. Med. Chem.* **1997**, *40*, 3584.

[2] Roglans, A.; Marquet, J.; Moreno-Manas, M. *Synth. Commun.* **1992**, *22*, 1249.

[3] Hirshfeld, A.; Taub, W. *Tertrahedron* **1972**, *28*, 1275.

[4] Augustine, R. L.; Zelawski, Z. S.; Rzalarek, D. H. *J. Org. Chem.* **1967**, *32*, 2257.

[5] Zhou, C. Y.; Yu, W. Y.; Chan, P. W. H.; Che, C. M. *J. Org. Chem.* **2004**, *69*, 7072.

[6] Clark, J. S.; Hodgson, P. B.; Goldsmith, M. D.; Street, L. J. *J. Chem. Soc. Perkin Trans1* **2001**, *24*, 3312.

[7] Augustine, R.L.; Zelawski, Z.S.; Malarek, D.H. *J. Org. Chem.* **1967**, *32*, 2257.

[8] Leonard, N.J.; Fischer, F.E.; Barthel, E.; Figueras, J.; Wildman, W.C. *J. Am. Chem. Soc.* **1951**, *73*, 2371.

[9] Zvonok, A. M.; Biba, V. I.; Stanishevskii, L. S. *Chem. Heterocycl. Compds.* **1988**, *24*, 1113.

[10] Zvonok, A.M.; Biba, V.I.; Stanisheveskii, L.S. *Khim. Geterotsikl. Soedin.,* 1988,10,1344; *Chem. Abstr*. **1989**, *111*, 39162q.

[11] Cavalla, J.F. *J. Chem. Soc.* **1962**, 4664.

[12] Hennion, G. F.; King G. G. *J. Chem. Eng. Data* **1967**, *12*, 275.

[13] Collina, S.; Rossi, D.; Loddo, G.; Barbieri, A.; Lanza, E.; Linati, L.; Alcaro, S.; Gallelli, A.; Azzolina, O. *Bioorg. Med. Chem.* **2005**, *13*, 3117.

[14] Cavall, J. F.; Davoll. J.; Dean, M. J.; Franklin, C. S.; Temple, D. M., *J. Med. Pharm. Chem.* **1961**, *4*, 1.

[15] Ryan, C.W.; Ainsworth, C. *J. Org. Chem.* **1962**, *27*, 2901.

[16] Yamazaki, T.; Matoba, K.; Isomura, K.; Nagata, M.; Castle, R.N. *J. Heterocyclic Chem.* **1974**, *11*, 503.

[17] Eicher, T.; Weber, J. L. *Tetrahedron Lett.* **1974**, *15*, 1381.

[18] Westerlund, A.; Gras, J. L.; Carlson, R. *Tetrahedron* **2001**, *57*, 5879.

[19] Lunsford, C.D. Patent 2,878,264, 1959; *Chem. Abstr.***1959**, *53*, 15096F.

[20] Casy, A.F.; Birnbaum, H.; Hall, G. H.; Everitt, B J. *J. Pharm. Pharmacol.* **1965**, *17*, 157.

[21] Shen, R.-P; Pi, S.; Xia, W.; Zhao, G.; Wang, G.; Chen, X.; *Gaoxiao Huaxue Gongcheng Xuebao* **2003**, *17*, 438; *Chem. Abstr.* **2004**, *140*, 95872g.

[22] Cavalla, J. F.; Davoll, J.; Dean, M. J.; Franklin, C. S.; Temple, D.M.; Wax, J.; winder, C.V. *J. Med. Pharm. Chem.* **1961**, *4*,1.

[23] Levisalles, J.; Rose, E. *Bull. Soc. Chem. Fr.* **1976**, *11*, 1947.

[24] Julia, M.; LeGoffie, F.; Igolen, J. *Bull. Soc. Chim. Fr.* **1969**, *9*, 3290; *Chem. Abstr.* **1970**, *72*, 21553J.

[25] Gensler, W. J.; Hu, M.W. *J. Org. Chem.* **1973**, *38*, 3848.

[26] Sheradsky, T.; Southwick, P. L. *J. Org. Chem.* **1965**, *30*, 194.

[27] Carelli, V.; Morlacchi, F. *Ann. Chim. (Rome),* **1964**, *54*, 1291; *Chem., Abstr.* **1965**, *62*, 11769h.

[28] Tomishige, M. *Chem. Pharm. Bull. (Tokyo)* **1961**, *9*, 818

[29] Sasaki, H. *Nippon Kagaku Zasshi,* **1955**, *76*, 35; *Chem. Abstr.* **1957**, *51*, 17878e.

[30] Moyer, M. P.; Feldman, P. L.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 5223.

[31] Blake, J.; Willson, C.D.; Rapoport, H. *J. Am . Chem. Soc.* **1964**, *86*, 5293.

[32] Ohsawa, T.; Ihara, M.; Fukumoto, K.; Kametani, T. *J. Org.* Chem. **1983**, *48*, 3644.

[33] Kuhn, R.; Osswald, G. *Chem. Ber.* **1956**, *89*, 1423.

[34] Geissman, T. A.; Waiss, A. C. *J. Org. Chem.* **1962**, *27*, 139.

[35] Wu, Y.H.; Feldkamp, R.F.; Lobeck, W.G. U.S. 3, 083, 208, 1963; *Chem. Abstr.* **1963**, *59*, 8709b.

[36] Miyamoto, M. *Yakugaku Zasshi* **1957**, 77, 568; *Chem. Abstr.* **1957**, *51*, 16422e.

[37] Tatsuoka, S.; Tanaka, K.; Ueno, S.; Miyamoto, M.; Mitsuno, Y.; Uchibayashi ,S. Patent 10,509, 1960; *Chem. Abstr.* **1961**, *55*, 9429f.

[38] Ablordeppey, S. Y.; Lyles-Eggleston, M.; Bricker, B.; Zhang, W.; Zhu, X.; Goodmana, C.; Roth, B. L. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3219.

[39] Taylor, E. C.; Ahmed, Z.; Robkes, D. J.; Kempton, R. J. *J. Org. Chem.* **1991**, *56*, 5443.

[40] Taylor, E. C.; McDaniel, K.; Skotnicki, J. S. *J.* Org. *Chem.* **1984**, *49*, 2500.

[41] Taylor, E. C.; Fletcher, S. R.; Fitzjohn, S. *J. Org. Chem.* **1985**, *50*, 1010.

[42] Padwa, A.; Matzinger, M.; Tomioka, Y.; Venkatramanan, M. K. *J. Org. Chem.* **1988**, *53*, 955.

[43] Jernow, J.; Tautz, W.; Rosen, P.; Williams, T. H. *J. Org. Chem.* **1979**, *44*, 4213.

[44] Su, T.L.; Watanabe, K.A. *J. Org. Chem.* **1989**, *54*, 220.

[45] Southwich, P. L.; Madhav, R.; Filzgerald; J. A. *J. Heterocycl. Chem.* **1969**, *6*, 507.

[46] Southwich, P. L.; Sapper, D. I.; Pursglove, L. A. *J. Am. Chem. Soc.* **1950**, *72*, 4940.

[47] Southwich, P. L.; Dimond, H. L. *J. Am. Chem. Soc.* **1954**, *76*, 5667.

[48] Barvinok, M. S.; Kuprin, V. S.; Mazurek, V.V.; Semenov, G.I. *zhur. Obshcheĭ Khim.* **1961**, *31*, 632; *Chem. Abstr.* **1961**, *55*,

22285q.

[49] Parpani, P.; Zecchi, G. *J. Org. Chem.* **1987**, *52*, 1417.

[50] Huang, Y.-L.; Lin, C.-F.; Lee, Y.-J.; Li, W.-W.; Chao, T.-C.; Bacherikov, V. A.; Chen, K.-T.; Chen, C.-M.; Su, T.-L. *Bioorg. Med. Chem.* **2003**, *11*, 145.

[51] Daidouji, K.; Fuchibe, K.; Akiyama, T. *Org. Lett.* **2005**, *7*, 1051.

[52] Black, D.C.; Boscacci, A. B. *Aust. J. Chem.,* **1976**, *29*, 2511.

[53] Garst, M. E., Bonfiglio, J. N., Grudoski, D.A.; Marks, J. *J. Org. Chem.* **1980**, *45*, 2307.

[54] Cum, G.; Sindona, G.; Uccella, N.; *Chim. Ind. (Milan),* **1976**, *58*, 384; *Chem. Abstr.* **1977**, *86*, 290759.

[55] Lunsford, C. D.; Ward, J. W.; Pallottat, A. J.; Tusing, T. W.; Rose, E. K.; Murphey, R. S. *J. Med. Pharm. Chem.* **1959**, *1*, 73.

[56] Kizaki, N.; Yasohara, Y.; Nagashima, N.; Hasegawa, J. *Journal of Molecular Catalysis B: Enzymatic* Accepted **2007**.

[57] Hanna, P. E.; Ahmed, A.E. *J. Med. Chem.* **1973**, *16*, 963.

[58] Bridgeman, E.; Cavill, J. L.; Schofield, D. J.; Wilkins, D. S.; Tomkinson, N. C. *Tetrahedron Lett.* **2005**, *46*, 8521.

[59] Nazarski, R.; Skolimowski, J.; Skowronski, R.; *Pol. J. Chem.* **1979**, *53, 821; Chem. Abstr.* **1979**, *91*, 211181b.

[60] Davis, P.; Cavella, J. F.; Davoll, J. Brit. 862,513**,** 1961; *Chem. Abstr.* **1961**, *55*, 19950h.

[61] Zhang, Y.; Ran, C.; Zhou, G.; Sayre, L. M. *Bioorg. Med. Chem.* **2007**, *15*, 1868.

[62] Naylor, A.; Judd, D. B.; Lloyd, J. E.; Scopes, D. I. C.; Hayes, A. G.; P. J. Birch. *J. Med. Chem.* **1993**, *36*, 2075.

[63] Amer, F. A.; Hammouda, M.; El-Ahl, A.A.S.; Abdel-Wahab, B.F. *J. Chin. Chem. Soc.* **2007**, *54*, 1543.

[64] Lagrange, A.; Forestier, S.; Lang, G.; Luppi, B. Patent 3,931,269, 1990; *Chem. Abstr.* **1990**, *113*, 131982w.

[65] Hofmann, T. *J. Agric. Food Chem.* **1998,** *46,* 3902.

[66] Yamaji, M. Patent 01,301,655, 1989; *Chem. Abstr.***1990**, *112*, 198123q.

[67] Iwanami, S.; Takashima, M.; Hirata, Y.; Hasegawa, O.; Usuda, S. *J. Med. Chem.* **1981**, *24*, 1224.

[68] Iwanami, S.; Takashima, M. Patent 78 28,161, 1978; *Chem. Abstr.* **1978**, *89*, 43107v.

[69] Han, C.; Kim, S, J.; Kwak, H. S.; Lee, S. H.; Park, T, H.; Sung, Gil, Y. Patent 3,786, 2002; *Chem. Abstr.* **2005**, *142*, 113882h.

[70] Hwang, G. H.; Kim, Y. D.; Nam, H.; Chang, J. H.; Shin, H. I.; Kim, Y. K., Lee, K. H.; Le, J. S.; Noh, H.K. Patent 92, 129, 2004; *Chem. Abstr.***2004**, *141*, 379800c.

[71] Theiry, V.; Guillaumet, G.; Andre, P. Patent 2,673,626, 1992; *Chem. Abstr.* **1993**, *118*, 81435a.

[72] Reznikov, V.A.; Kishnevetskaya, L.A.; Volodarskii, L. B.; *Izv. Akad. Nauk. SSSR, Ser. Khim.* **1990**, *2*, 395; *Chem. Abstr.* **1990**, *113*, 23597r.

[73] Aksanova, L.A.; Kucherova, N. F.; Sharkova; L.M. *Khim. Geterotsikl. Soedin,* **1969**, *6*, 995; *Chem. Abstr.* **1970**, *72*, 121398f.

[74] Sharkova, N. M.; Kucherova, N. F.; Aksanova, L. A.; Zagorevskii, V. A. *Chem. Heterocycl. Compds.* **1969**, *5*, 66.

[75] Smith, L. I.; Opie, J. W. *Org. Syn.* **1948**, *28*, 11.

[76] Kepler, J. A.; Wani, M. C.; McNauil, J. M.; Wall, M. E.; Levine S. *G.*
J. Org. Chem. **1969**, *34*, 3853.

[77] Wani, M. C.; Wall, M. E. *J. Org. Chem.* **1969**, *34*, 1364.

[78] Peng, H.; Kim, D.; Sarkaria, J. N.; Cho, Y.-S.; Abraham, R. T.; Zalkow, L. H. *Bioorg. Med. Chem.* **2002**, *10*, 167.

[79] Griss, G.; Hurnaus, R.; Grell, W.; Sauter, R.; Leitold, M.; Reichl, R.Patent 2, 521, 544, 1976; *Chem. Abstr.* **9717**, *86*, 72619g.

[80] Khan, M. A.; Ferreira, R. J. *Heterocycles,* **1977**, *6*, 1927.

[81] Amer, F. A.; Hammouda, M.; El-Ahl, A.A.S.; Abdel-Wahab, B.F. *Synth. Commun.* **2008**, in press.

[82] Wille, E.; Luettke, W. *Liebigs Ann. Chem.* **1980**, *12*, 2039.

[83] Yamazaki, T.; Matoba, K.; Isomura, K.; Nagata, M.; Castle, R. N. *J. Heterocyclic Chem.* **1974**, *11*, 503.

[84] Tsutamune, T. Patent 02, 258, 763, 1990; *Chem. Abstr.* **1991**, *114*, 185260y.

[85] Naylor, A.; Judd, D. B.; Scopes D. I. C.; Hayes, A. G.; Birch, P. J. *J. Med. Chem.* **1994**, *37*, 2138.

[86] Plouvier, B.; Beatch, G. N.; Jung, G. L.; Zolotoy, A.; Sheng, T.; Clohs, L.; Barrett, T. D.; Fedida, D.; Wang, W. Q.; Zhu, J. J.; Liu, Y.;Abraham, S.; Lynn, L.; Dong, Y.; Wall, R. A.; Walker, M. J. A. *J. Med. Chem.* **2007**, *50,* 2818.

[87] Bouygues, M.; Medou, M.; Chermann, J. C.; Camplo, M.; Kraus, J. L. *Eur. J. Med. Chem.* **1998**, *33*, 445.

[88] Courcambeck, J.; Bihel, F.; DeMichelis, C.; Quelever, G.; Kraus, J. L. *J. Chem. Soc., Perkin Trans.1* **2001**, *12*, 1421.

[89] Bouygues, M.; Medou, M.; Quelever, G.; Chermann, J.C.; Camplo, M.; Kraus, J. L. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 277.

[90] Chu, D.T.; Li, Q. Patent 5, 252, 747, 1993; *Chem. Abstr.* **1994**, *120*, 298462h.

[91] Bird, P.; Ellsworth E. L.; Nguyen, D. Q.; Sanchez, J. P.; Showalter, H. D. H.; Singh, R.; Stier, M. A.; Tran, T. P.; Watson, B. M.; Yip, J. Patent 01 53,273 ,2001; *Chem.Abstr.* **2001**, *135*, 122511u.

[92] Grinter, T. J.; Howie, S. Patent PCT Int. Appl. WO 01 17, 961, 2001; *Chem.Abstr.* **2001**, *134*, 222700c.

[93] Cho, S; Cho, M.; Hayler, J. D. Patent 01 18,002, 2001; *Chem.Abstr.* **2001**, *134*, 222702e.

[94] Iwanami, S.; Takashima, M.; Usuda, S. Patent 4, 210, 660, 1980; *Chem. Abstr.* **1980**, *93*, 220583c.

[95] Watanabe, K.A. Patent 4, 925, 939, 1990; *Chem. Abstr.* **1990**, *113*, 152462s.

[96] Edwards, P. N.; Large, M.S. Patent 586,229, 1994; *Chem. Abstr.* **1994**, *121*, 108501v.

[97] Tamazawa, K.; Kojima, T.; Arima, H.; Murakami, Y.; Isomura, Y.; Okada, K.; Takanobu, M.; Takenaka, T. Patent 160, 451, 1985; *Chem. Abstr.* **1987**, *106*, 4763f.

[98] The Merk Index of chemicals and drugs, 9th ed., Merk and Co. Inc. Rahway, N.J., U.S.A. 1976, Item no. 1031.

[99] Boswell, R.F.; Duncan, R.L. Patent 4, 139, 620, 1979; *Chem. Abstr.* **1979**, *90*, 168445f.

[100] Baker, R.; Bourrain, S.; Castro, P J.; Chambers, M. S.; Guiblin, A. R.; Hobbs, S.C.; Jelley, R. A.; Madin, A.; Matassa, V.G. Patent 96 04,274, 1996; *Chem. Abstr.* **1996**, *125*, 58520k.

[101] Effland, R. C.; Davis, L.; Klein, J. T. U.S.4, 268, 515, 1981; *Chem. Abstr.* **1981**, *85*, 150474h.

[102] Huryn, D. M.; Okabe, M. *Chem. Rev.* **1992**, *92*, 1745.

[103] Kraus, J. L.; Bouygues, M.; Courcambeck, J.; Chermann, J. C. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2023.

[104] Quelever, G; Bouygues, M; Kraus, J.-L. *J. Chem. Soc. Perkin Trans1* **2002**, *9*, 1181.

[105] Nadler, W.; Pupowicz, D. Patent 2005 82,848 100,773, 26, 2004; *Chem. Abstr.* **2005**, *143*, 267237j).

[106] Halazy, S.; Schwarz, M.; Quattropani, A.; Thomas, R.; Baxter A.; Scheer, P. Patent 01 72,705, 2001; *Chem. Abstr.* **2001**, *135*, 288686e.

[107] Halazy, S.; Schwarz, M.; Quattropani, A.; Thomas R.; Bomburn, A. Patent 01 106,033, 2001; *Chem. Abstr.* **2001**, *135*, 303763y.

[108] Jorand-Lebrun, C; Dorbais, J.; Quattropani, A; Schwarz, M.; Valognes, D. Patent 5, 249, 2004; *Chem. Abstr.* **2004**, *140*, 93917b.

[109] Schwarz, M.; Jorand-lebrun, C.; Valognes, D. Patent 2004 76,407, 2004; *Chem. Abstr.* **2004**, *141*, 24336y.

[110] Lee, D.; Kwon, Y; Kim, Y.; Rhee, C. Patent 02 18,336, 2002; *Chem. Abstr.* **2002**, *136*, 216642k.

[111] Beatch, G. N.; Choi, L. S. L.; Jung, G.; Liu, Y.; Plouvier B.; Wall, R.; Zhu, J.; Zolotoy, A.; Barrett, A. G.M. Patent PCT Int. Appl. WO 2004 99,137, 2004; *Chem. Abstr.* **2004**, *141*, 424107v.