INDOLES WITH C-3 AS SPIRO ATOM

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Abstract - This review article covers the synthesis, reactions and uses of spiro indoles with C-3 as spiro atom.

INTRODUCTION

The spiro carbon is a carbon atom shared by two ring systems. In this review, emphasis has been given only to those compounds in which C-3 of the indole ring is the spiro atom. This C-3 atom is shared by the indole ring and one another ring and therefore, leads to a variety of heterocyclic systems attached at C-3 of the indole ring. These spiro compounds have been investigated for various reasons viz :

(i) Various classes of these compounds may display different types of biological activities. Recently, Fredricamycin A has been discovered which is an anti-tumor-antibiotic agent. Fredricamycin A with a spiro system is expected to provide a lead to a new family of drugs.

(ii) There are various indole alkaloids with a C-3 spiro atom, and are synthesised from some simpler spiro indoles as reaction intermediates

(iii) The unexpected formation of spiro indoles is also observed during some cyclization and rearrangement reactions.

In this review article, we describe the synthesis, reactions and uses of spiro indoles with C-3 as spiro atom. The text has been classified in terms of various ring systems attached at C-3 of indole ring. For the present, naturally occurring indole alkaloids have not been covered.

I. ONE RING SYSTEMS

I-1) With No Heteroatom

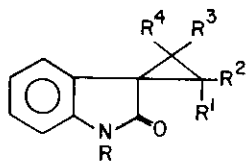
I-1.1) Cyclopropane

The base-induced alkylation of 3-unsubstituted oxindoles with 1-bromo-2-chloro-

ethane or 1,2-dibromoethane results in the formation of spiro[cyclopropane-1,3'-[3H]indol]-2'(1'H)-ones (1; R=R^1=R^2=R^3=R^4=H)[1-3]. 3-Bromoethylindoles cyclize in a similar manner in the presence of potassium carbonate to give spiro[cyclopropane-1,3'-indolines](2; R=H, COOMe)[4].

The title compounds of the type(1) have also been obtained by (i) the photolysis of 1-methyl-3-diazooxindoles in hexane (R=Me, R^1=R^2=Ph; R^3=R^4=H)[5] ; (ii) the thermolysis of the product obtained by reaction of 3-methyl-3-phenyl-2-oxindoles with diazomethane[6], or of indolyl tosylate[7] with potassium tert-butoxide; (iii) the pyrolysis of spiro[3H-indole-3,3'-pyrazolines](R=H, morpholinomethyl; R^1 = COOEt; R^2=R^3=R^4=H)[8] and (iv) the treatment of 3-phenylmethyleneindol-2-ones with $PhCOCH\overset{+}{S}Me_2$ (R=Ac, Me; R^1 = COPh; R^2=R^4=H; R^3 = substituted phenyl)[9].

Tryptamine methiodide, on treatment with lithium in ammonia[10] and various indole alkaloids, on vacuum distillation with calcium oxide, zinc dust and palladium, also yield spiro[cyclopropane-1,3'-[3H]indole] derivatives[11].



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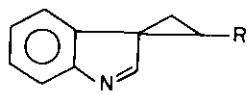

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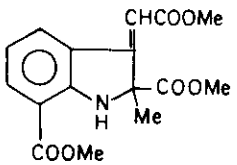

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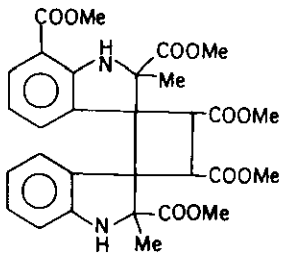

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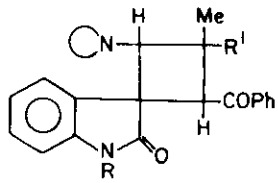

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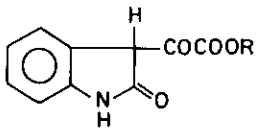

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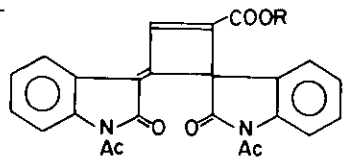

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Spiro[cyclopropane-1,2'-[2H]indol]-3'(1'H)-ones undergo Friedel Crafts reaction with acetic acid and trifluoroacetic anhydride giving spiro[cyclopropane-1,3'-[3H]indol]-2'(1'H)-ones (1; R=H, Ac; R^1=R^2=R^3=R^4=H) as a minor product[12].

Ir spectral studies[13] and antitubercular activity[14] have been reported in some cases; some compounds have been found useful as basic dyes[15,16].

I-1.2) Cyclobutane

3-Carboxymethyleneindole derivatives(3) photodimerizes to give spiro [cyclobutane-1,3'-[3 H]indole] derivatives(4)[17].

The spiro compounds(5; R=Me, Et; R^1=H,Me; ◯ = piperidino, pyrrolidino) have also been obtained by 1,2-cycloaddition reaction of N-alkyl substituted 3-oxindolideneacetophenones with enamines[18-20].

2-(2-Oxo-3-indolinyl)glyoxalates (6; R = Me, Et, CH_2Ph) undergo intramolecular Claisen condensation with acetic anhydride in the presence of pyridine to yield spiro[cyclobutane-1,3'-[3 H]indole] derivative(7) used as a purple pigment[21,22].

I-1.3) Cyclopentane

Base catalysed alkylation of 3-unsubstituted indol-2-one with 1,4-dibromobutane affords spiro[cyclopentane-1,3'-[3 H] indol]-2'(1'H)-one (8; R = Me; R^1, R^2=H; X=O)[23,24].

The following cyclization reactions have also been found to lead to the formation of the spiro compounds(8) viz; 3-(3-carboxypropyl)-1,2-dimethylindole with trifluoroacetic anhydride (R = Me; R^1 R^2 = O; X = $CHCOCF_3$)[25], cyclopentanecarboxylic acid phenylhydrazide with 20% hydrochloric acid(R=R^1=R^2=H; X=O)[26]; photocyclization of N-arylenamines (R=R^1=R^2=H; X = H, COOEt)[27]; 4,4-dialkylhomophthalimide with sodium hypochlorite in alkaline medium[28-30] and cyclization of $PhNRNHCOCHC_5H_9$[31].

Reactions of tetrahydrocarbazole derivatives with PPE or PPA[32], arene sulphonylazides[33-39], Grignard's reagent[40], oxidation with sodium metaperiodate[41], thallium diethylmalonate[42] and methanolic sodium hydroxide[43,44] also give rise to the above spiro derivatives.

The conversion of 4-(3-indolyl)-1-butanol into spiro products with potassium tert-butoxide[45] and $BF_3.Et_2O$[46] has also been reported. Spiro[cyclopentane-1,2'-ψindoxyls] with Grignard's reagent produce spiro[cyclopentane-1,3'-ψindoxyl] derivatives[40]. During dimerization of (E)-2-oxo-3-indolinylideneacetone, the formation of spiro cyclopentanes is also indicated[47].

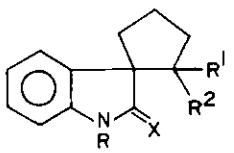
Various reactions like rearrangements[48-50], reduction[43,44], acetylation[43,44] and oxidation in presence of mercury lamp[51] of title compounds are reported in the literature. The crystal and molecular structure of 1'-methyl-2-(p-toluenesulfonamido)-2'-(p-toluenesulfonylimino)spiro[cyclopentane-1,3'-[3H] indole] [52]

and some other derivatives of this type[53,54] have been studied by various workers.

Some of the compounds have been used as basic dyes[15,16] and biological activities like antiinflammatory[31], antidepressant[55] and antihypertensive[41] have been reported to be associated with these structures.

I-1.4) Cyclohexane

Spiro[cyclohexane-1,3'-[3H]indole] derivatives(9) have been synthesized using various cyclization reactions, viz; (i) Treatment of 1-phenylindol-2-one with methyl acrylate followed by cyclization[56], (ii) Fischer indole cyclization of phenyl hydrazone of acetylhexane with zinc chloride[57], (iii) Cyclization of 1-methyl-3,3-di(β-carbethoxyethyl)oxindole with potassium in toluene[58], (iv) Alkylation of 2-oxindoles with 1,5-diiodopentane in presence of butyl lithium[59], (v) Diels-Alder reaction of 3-methoxycarbonylmethyleneindol-2-ones with $RCH{=}CH{-}CH{=}CH_2$ (R=Me, OAc)[60], (vi) Cyclization of cyclohexane carbohydrazide with calcium oxide and hydrochloric acid[26,61], (vii) Reaction of substituted phenyl isocyanide with cyclohexanone in presence of BF_3 or BF_3 etherate[62-64], (viii) Cyclization of 1-phenyl-2-acylhydrazine with phosphorus oxychloride[65], (ix) Reaction of tetracyanoethylene with the cyclic adduct obtained by treatment of 3-oxindolidene acetophenone with enamines[66], (x) Reaction of 4,4-dialkylhomophthalimide with sodium ethoxide in alkaline medium[28-30], and (xi) Cyclization of $PhNRNHCOCHC_6H_{11}$[31].



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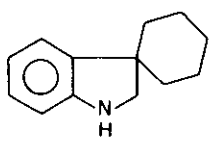

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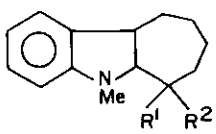
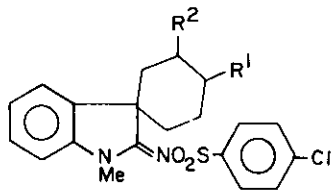


(10)

R^1= OH, R^2=H; R^1=R^2=H

R^1=R^2=OH; R^1=NH_2, R^2=H



(11)

R^1=OH, R^2=H ; R^1=R^2=H

R^1=R^2=OH ; R^1=NH_2, R^2=H

Hexahydrocycloheptaindoles(10) on treatment with p-chlorobenzenesulphonyl azide give spiro[cyclohexane-1,3'-[3H]indoles](11)[38,67,68].

Some reactions of the title compounds have also been studied[58].

A number of compounds have been used as analgesics[56], fungicides[69-71], antidepressants[55] and antiinflammatory agents[31].

Furthermore, various derivatives are useful as basic dyes[15,16], as dye developers for photographic diffusion transfer system[72] and as photochromic agents[73]. Some dyes of this series (merocyanine-rhodamines) have been studied with respect to the changes in absorption, fluorescence, dichroism and birifringence in stained giant axons[74].

I-1.5) Cycloheptane

Hexahydrotolylsulphonylaminocyclooct[b]indole obtained by the reaction of hexahydrocyclooctindole with tosylazide on shaking with platinum black in acetic acid yielded 2-p-tolyl-sulphonylaminospiro[cycloheptane-1,3'-[3H]indole][67].

I-2) With One Heteroatom

I-2.1) Oxirene

The syntheses of spiro[3H-indole-3,2'-oxiran]-2(1)-ones(12) have been carried out in various ways from isatin and its derivatives :

(i) By the reaction of isatin with diazomethane or diaryldiazomethane(Ph_2CN_2) (12; R=H,Me,Ph; R^1,R^2=H,H; Ph,Ph; R^3=H)[75,76].

(ii) Epoxidation of 3-disubstituted methyleneoxindoles with hydrogen peroxide in presence of basic catalyst (12; R=H,Me; R^1=Me,Ph; R^2=Me,Ph; i-Pr, 4-Py; R^3=H)[77-81].

(iii) By the reaction of hydrogen peroxide on 3-aroylmethyleneindol-2-ones or indolo[2,3-c]pyridazines (12; R=H,Me; R^1=H; R^2=substituted benzoyl; R^3=H,OMe)[82,83].

(iv) By the reaction of isatin with o-nitrobenzyl chloride (12; R=R^1=R^3=H; R^2=o-nitrobenzyl)[84].

The reaction of 2-(methylthio)indolin-3-ones with diazomethane affords 2-methylthio-spiro[3H-indole-3,2'-oxiranes](13)[85,86]. Sulphur ylides also produce these compounds with isatin[87].

Some reactions of these indoles and their rearrangements into 2,3-disubstituted indoles have been described by Anthony[77]. The compounds (12; R^2=benzoyl) react with hydrazine derivatives affording spiro[3H-indole-3,3'-pyrazolidine] derivatives[82,83,88].

The biological activities such as diuretic, tranquilizing, anticonvulsant, transaminase inhibiting, blood platelet agregation, fungicidal and bactericidal are associated with these compounds[78,80,81,83,89].

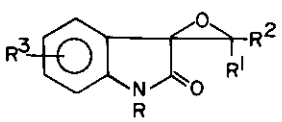
I-2.2) Azete

Hassan and co-workers[90-94] have reported the synthesis of spiro [azetidine-2,3'-[3H]indol]-2',4(1'H)-diones (15) by the reaction of 3-isatylidene anil derivatives(14) with phthalylglycyl chloride or chloroacetyl chloride and the compounds have been further subjected to different reactions.

The formation of these β-lactams has also been shown on tlc plates using the same reactants[95].

I-2.3) Oxete

The thermal 2+2 cycloaddition of $(MeO)_2C{:}CH_2$ to 2-ethoxy-3-indolone (16) at 40°C has resulted in the regiospecific formation of 2-ethoxy-4',4'-dimethoxy-spiro [3H indole-3,2'-oxetane](17)[96].



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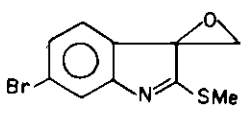

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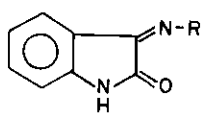
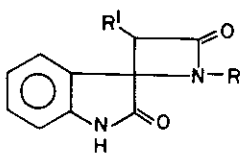


(14)

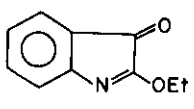
R = Aryl , heterocycle



(15)

R = Aryl , heterocycle

R' = Phthalyl , Cl , NH_2



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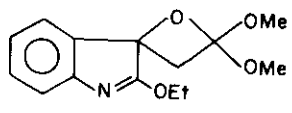


(17)

I-2.4) Pyrrole

Spiro[3H-indole-3,3'-pyrrolidines](18) were first prepared from tryptamine/ tryptophan derivatives and few examples are cited here :

(i) Pictet-Spengler type condensation of 3-(2-aminoethyl)-2-oxindole with appropriate aldehyde[97-99].

(ii) The reaction of 3-(2-aminoethyl)indole with aldehyde or NBS[100,101].

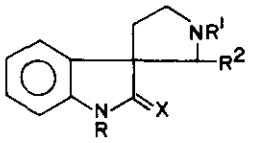
(iii) The condensation of 2-hydroxytryptamine hydrochloride with hemiacetals of tetrahydropyran-2-ol in presence of sodium acetate[102].

(iv) The condensation of 2-hydroxytryptamine hydrochloride with 3-oxobutanol ethyleneketal in basic aqueous ethanol[103].

(v) The reaction of methyltryptophan with excess formaldehyde and H ions in the presence of Raney nickel or 5% Pd/C[104].

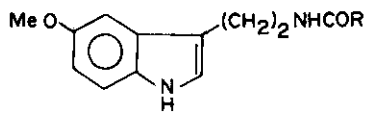
The treatment of melatonin derivatives(19) with pentafluoropropionic anhydride affords spiro products(20)[105].

The formation of spiro-pyrrolidines has been reported during the treatment of Mannich bases of indoles with HCl followed by hydrogenolysis[106].



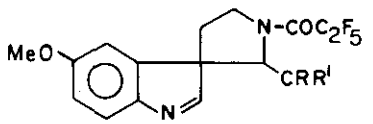
(18)

R = H, CH_2OH, CH_2OAc, CH_2OBz;
R^1 = H, Bz, Ac, $COCMe_3$;
R^2 = H, Et, Pr, 3,4-$(OMe)_2C_6H_3$, 3-OH,4-OMe C_6H_3
X = H_2, O



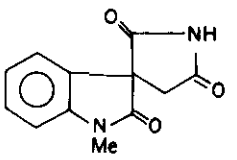
(19)

R = Me, Pr, $CHMe_2$



(20)

R = R^1 = Me
R = H, R^1 = Me
R = H, R^1 = Et



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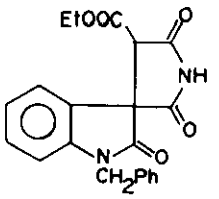

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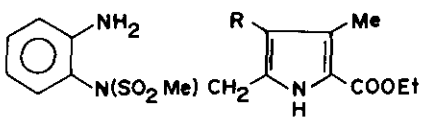
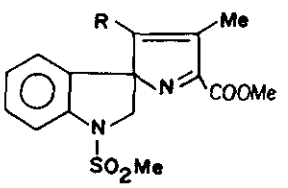


(23)

R = Ac, COOEt



(24)

R = Ac, COOEt

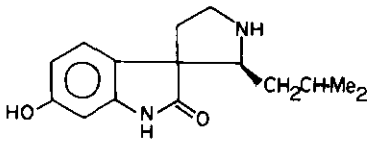
In another approach, 1-substituted isatins have been condensed with cyanoethyl ester followed by the reaction of KCN/HCN to give spiro products 21 and 22 [107,108].

Tetrahydro-β-carbolines have also been successfully converted into corresponding spiro products with different reagents, e.g. (i) tert-butyl hypochlorite and methanolic sodium hydroxide[109,110], (ii) arenesulphonyl azides[111-113] and (iii) osmium tetraoxide[34].

Copper catalysed decomposition of diazonium salt of compounds (23) has been reported to give spiro indolines(24)[114,115].

During the cyclization of benzylidene tryptamines into tetrahydro-β-carbolines, the formation of spiro[indoline-3,3'-pyrrolidines] has been found as intermediate[116].

The syntheses of some specific compounds of this series such as (25) from 2,5-Cl(OMe)$C_6H_4NH_2$ and NC-CH=CH-COOH via a complex of $(Ph_3P)_3Ni$ and aryl halide[117], (26) by the photocyclization of N-arylenamines[27], (27) and (28) from 3-(2-aminoaryl)-1-benzylpyrrolidine-2,5-diones in the presence of catalytic amount of alkoxide[118,119] and (29)[120] have been reported by various workers.



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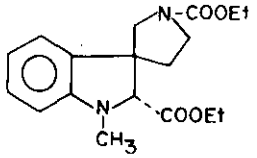

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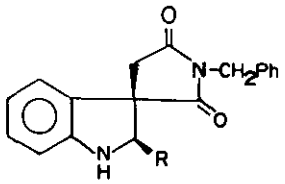

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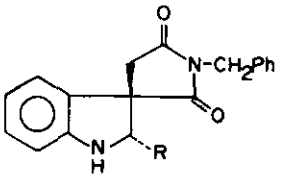

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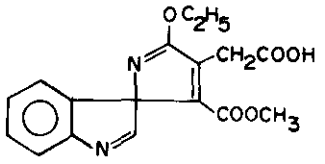


(29)

R = Ph , p-OMe C_6H_4 , Pr , 2-pyrrolyl , Me_3C , etc.

A number of spiro[indole-pyrrolidines] exhibit local anesthetic activity[100],

anticonvulsant activity[108], binding affinity to glycine receptors[109] and other pharmacological activities[111].

I-2.5) Furan

Spiro[furan-2,3'-[3H]indol]-2'(1'H)-one derivatives(30) have been synthesized from indole-3-propanols[121,122] or indole-3-propionic acids[123,124] by their reaction with NBS/NCS. Indole-3-propionic acids can also be cyclized with thallium(III) nitrate to give similar compounds[125]. 2-(2-Nitrophenylsulphonyl)indole-3-propionic acid with NBS gives spiro indoline(31)[126].

Dipeptides of indole with NBS also give similar compounds[127]. Various tryptophan derivatives are frequently oxidized to spiro furans, e.g. (i) oxide of 2-tryptophan with Me_3C-COOH in presence of ferrous sulphate(30; R=NH_2, X=O)[128], (ii) tryptophan on oxidation with DMSO-HBr and chromium trioxide[129,130], (iii) N-α-acetyltryptophan with NBS and tert-butanol (30; R=NHAc, X=O)[131] and (iv) N-phthaloyltryptophan with NBS and tert-butanol (30; R=phthaloyl, X=O)[129,132].

1-Methylisatin on condensation with $BrCH_2C(:CH_2)CO_2Et$ gives (32)[133] and with glyoxalbisulphite and sodium cyanide in aqueous sodium carbonate gives (33)[134]. Acetylation of compound (33) followed by ring opening and subsequent cyclization affords pyranoindoles[135]. Compounds (32) have exhibited anti P-338 lymphocytic leukemia activity[133] and some other spiro-furans are active as antiinflammatory[132], CNS[132,136] and antihypertensive drugs[41].

I-2.6) Thiophene

Hino et al.[121,122] have reported the synthesis of 4',5'-dihydro-spiro[3H-indole-3,2'(3'H)-thiophene]-2(1H)-one (34) by the action of NBS/NCS on indole-3-propanethiol.

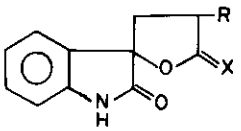
3-(2-Substituted indolyl)thioacrylates (35) undergo cyclization in the presence of HCl-MeOH to give spiro-thiophenes (36)[137].

Reaction of 1,3,4,5-tetrahydro-5-methylthiopyrano[4,3-b]indole with arene sulphonyl azides yields 3-iminoindolin-2-spiro-thiacyclopentane and 2-imino-indolin-3-spiro-thiacyclopentane[138].

Treatment of 3-(3-methyl-2-oxobutyl)-3-hydroxyoxindole with thionyl chloride gave an unexpected product identified as 3'-chloro-5',5'-dimethyl-spiro[3H-indole-3,2'(3'H)-thiophene]-2,4'(1H,5'H)-dione-1'-oxide (37)[139].

I-2.7) Pyridine

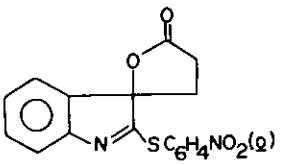
2-Oxindoles, when treated with sodamide and $RN(CH_2CH_2Cl)_2$, produced the corres-



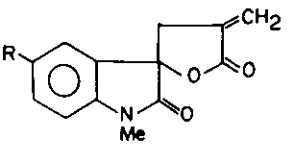
(30)

X = H_2, O

R = H, NHAc, NH_2, phtholoyl

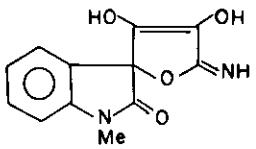


(31)

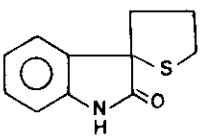


(32)

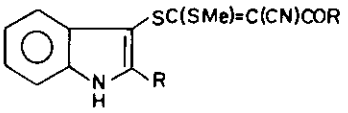
R = H, I



(33)



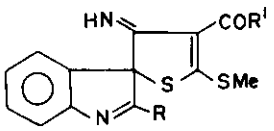
(34)



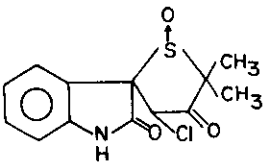
(35)

R = H, Me, Ph

R' = OMe, NH_2, $NHNH_2$, $NHCH_2$- 



(36)



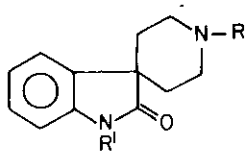
(37)

ponding spiro[3H-indole-3,4'-piperidin]-2(1H)-ones (38)[140]. A large number of various derivatives of this type possessing biological activity have been synthesized[141-143]. During the Fischer indole cyclization of phenylhydrazone of 4-acetylpiperidine with zinc chloride, spiro indolines are frequently obtained[57]. The condensation of the derivative of phenacyl cyanide with $(ClCH_2CH_2)_2NMe$ followed by cyclization affords spiro[3H-indole-3,4'-piperidines] (39)[144-148]. Kornet and Thio[100] have prepared spiro[3H-indole-3,2'-piperidine]-2(1H)-ones from 3-(3-aminopropyl)-2-oxindole and NBS. A few spiro[3H-indole-3,3'-piperidines] have been reported from 3-(3-aminopropyl)indole and an aldehyde[101]. Cyano derivative of 2-oxindoles (40), on reaction with hydroxylamine hydrochloride, affords the spiro derivative (41)[149].

Some spiro-dihydropyridines have been obtained from acylation of imines[150] and naphthyridines[151] with 4-pyridine-carbonyl chloride. Spiro-piperidines (43; R^2= arylsulphonyl) are also obtained by the reaction of arene sulphonyl azides on

tetrahydrocarbolines (42)[38].

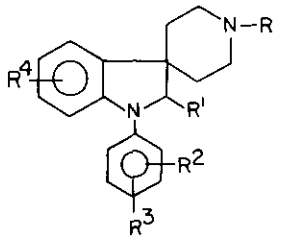
These compounds are of great biological importance and have shown anticonvulsant, antidepressant, tranquilizing, central nerve inhibiting, analgesic, antihypertensive, antirheumatic, local anesthetic, hypotensive, antiinflammatory and ganglion blocking activities[100,141-148,152].



(38)

R = Subs. phenyl alkyl, alkyl, phenoxyalkyl, benzoylalkyl, phenyl, phenylalkenyl, etc.

R^1 = H, Ph, alkoxy, C_{1-4} alkyl, etc.



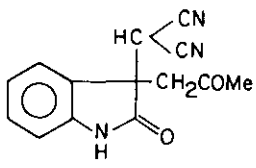
(39)

R = H, alkyl, cyanoalkyl, COOPh, phenylalkyl

R^1 = H, alkyl

R^2, R^3 = (Same or different) H, halo, OH, NH_2, CF_3, NO_2, NHAc, alkyl, aryl

R^4 = H, halo, OH, alkyl, alkoxy



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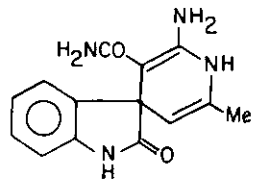
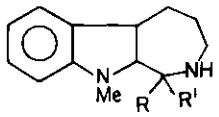


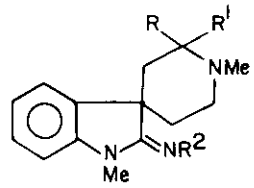
(41)



(42)

R = R' = H

RR' = O



(43)

I-2.8) Pyran

5-Bromo-4',5'-dihydro-spiro[3H-indole-3,2'-[2H]pyran]-2,6'(1H,3'H)-dione (44) has been obtained during the reaction of indole-3-butyric acid with NBS[153].

Spiro[3H-indole-3,4'-[4H]pyran]-2(1H)-ones (45) are synthesized by Michael condensation of 3-cyano-indol-2-one or 3-carbethoxymethylene-indol-2-one with 1,3-diketones[154] and (46) by the reaction of the Michael adduct of acetophenone/acetone with 3-cyanomethyleneoxindoles followed by reaction with $NaBH_4$[149].

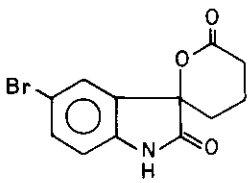
The reaction of compound (47) with isonicotinic acid through various steps has afforded the spiro product (48) which is hypnotic and muscle relaxant[155].

Some of these compounds, useful as antiinflammatory agents, have also been synthesized[141].

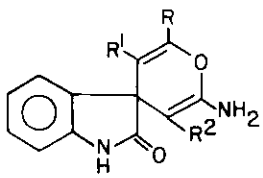
I-3) With Two Heteroatoms

I-3.1) Diazirine

The irradiation of 3-diazoindol-2-one (49) at $\lambda > 290$ nm in methanol, in the early



(44)

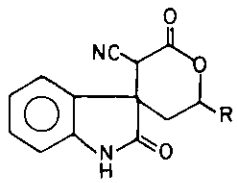


(45)

R = Me , Ph , COOMe

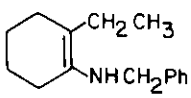
R^1 = H, Ac , Bz, COOEt

R^2 = CN , COOEt

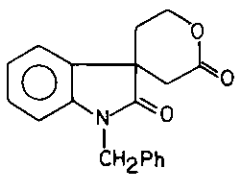


(46)

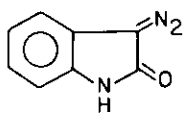
R = Me , Ph



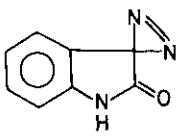
(47)



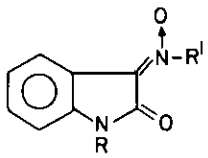
(48)



(49)

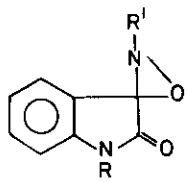


(50)



(51)

R = H, Me ; R^1 = Me , Ph



(52)

stages, has produced spiro[3H-diazirine-3,3'-[3H]indol]-2'(1'H)-one (50)[156]. The kinetics of the valence isomerization of (49) to (50) were detected at 18.5-53.4° and activation parameters have been reported. Theoretical paths of ring closure and ring opening have also been discussed[157].

I-3.2) Oxazirine

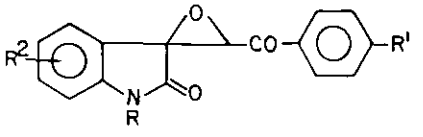
During the photolysis of nitrones of isatin (51) spiro[3H-indole-3,3'-oxaziridin]-2(1H)-ones (52) are reported to have been formed[158].

I-3.3) Pyrazole

Various isatin derivatives such as spiro[2-oxindole-3,2'-(3-substituted)oxiranes] (53)[82,83,88], butenolides (54) obtained from isatin and β-aroylpropionic acids[159] and 3-aroylmethyleneindol-2-ones (55)[94,160,161] cyclize with hydrazine hydrate to afford spiro[3H-indole-3,3'-pyrazolin]-2-ones.

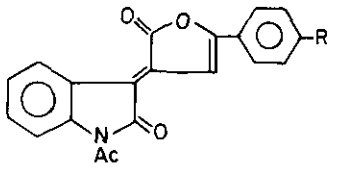
Various 3-substituted 2-oxindoles with diazomethane frequently give spiro[3H-indole-3,3'-pyrazolin]-2-ones (56 and 57)[6,8,17].

An attempted synthesis of title compounds from nitrile substituted indoline Δ^3-α-acrylates and diazoalkanes was unsuccessful[161].



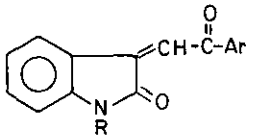
(53)

R = H, Me ; R' = H, Br, Cl, OMe ;
R^2 = H, Me, OMe



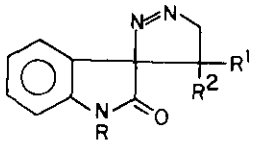
(54)

R = H, Me, Cl



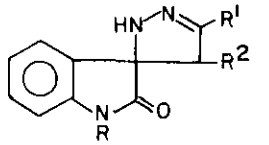
(55)

R = H, Me



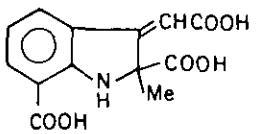
(56)

R = H, Me, Ac
R', R^2 = Me, NO_2, H, COOEt

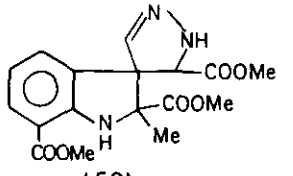


(57)

R = H, Me, Ac
R', R^2 = Me, NO_2, H, COOEt



(58)



(59)

A tricarboxylic acid derivative (58), obtained from pyruvic acid and anthranilic acid, on treatment with diazomethane, afforded spiro-pyrazoline (59)[17].
These compounds have been found useful as analgesic[88], antiphologistic[88] and blood platelet aggregators[89].

I-3.4) Imidazole

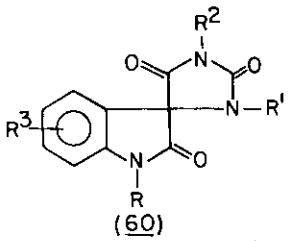
The synthesis of spiro[imidazolidine-4,3'-[3H]indole]-2,2',5(1'H)-triones(60) has been reported from the corresponding isatin, potassium cyanide and ammonium carbonate and the compounds have been used in treating complications of diabetes or galactosemia[162-164].

I-3.5) Oxazole and Isoxazole

Dioxindole-3-carboxyureides (61), on addition of 50% aqueous potassium hydroxide, liberate ammonia and produce spiro[3H-indole-3,2'-oxazolidine]-2,3',5'(1H)-triones (62). The alkylation of (62) affords N-alkylated derivatives[165].
The condensation of 3-aroylmethyleneindol-2-ones with benzaldoximes has yielded spiro[3H-indole-3,5'-[2]isoxazolin]-2-ones (63; R=H,Me; R^1= substituted phenyl; R^2=substituted benzoyl)[166] and 3-methylene ester of indol-2-one produces (63; R=H,Me; R^1=Ph; R^2=CO_2Et) with phenyl cyanate[8].
Synthesis and properties of some polymers containing spiro[indoline-isoxazoline] system have also been reported[168].
These compounds are useful as CNS drugs[166], antiinflammatory agents[166] and blood platelet aggregators[89].

I-3.6) Thiazole

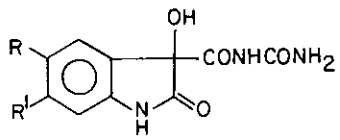
The synthesis of spiro[3H-indole-3,2'-thiazolidine]-2,4'(1H)-diones (65) has been carried out by the condensation of isatin-3-anils with mercaptoacetic acid[90-93,169]. The compounds have also been directly obtained from isatin,amines and mercaptoacetic acid without isolation of isatin-3-anils[170,171]. The compounds have successfully undergone acetylation, chloroacetylation and Mannich reaction[170]. The condensation of isatin with β-mercaptoethylamine hydrochloride also affords the same spiro products[172,173]. Direct condensation of isatin with N-(2-thiophenylmethyl)-1,3-thiazolidine-2,4-dione produces the spiro product, 3'-(2-thiophenylmethyl)-spiro[3H-indole-3,5'-thiazolidine]-2,2',4'(1H)-trione[174].
Rovnyak et al.[175] have prepared the spiro compound (66) from oxindole and chloroethyl isothiocyanate in glyme containing sodium hydride.



(60)

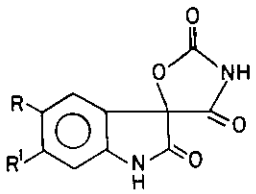
R = H, alkyl, CH_2Ph, aryl; R^1 = H, Me

R^2 = H; R^3 = H, OH, NO_2, halo, alkyl



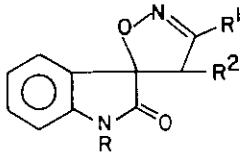
(61)

R, R^1 = H or Me

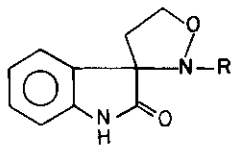


(62)

R, R^1 = H or Me

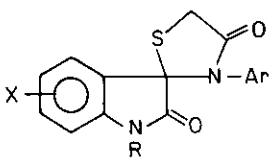


(63)



(64)

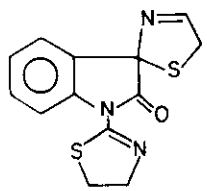
R = Ph, 4-Cl C_6H_4, 4Me_2N-C_6H_4



(65)

X = H, F, CF_3; Ar = Subs. phenyl

R = H, alkyl, acyl, morpholinomethyl



(66)

These products are useful as pharmaceuticals, antiinflammatory agents[173,175], fungistatic[174], bacteriostatic[174] and antiradiators[172].

I-3.7) 1,3-Dioxole

The synthesis of spiro[1,3-dioxolane-2,3'-[3H]indol]-2'(1'H)-ones(67) involves the condensation of isatin with 1,2-diols in the presence of p-toluenesulphonic acid or oxalic acid[176,177]. Some other derivatives (R=2-propynyl)[178] and (X=5-I)[179] have also been prepared.

Mass spectral characteristics have been reported by Zhungietu et al.[180]. Spiro-[dioxolane-indolines]can easily be alkylated at nitrogen atom[181,182]. 2'-Oxo-spiro[1,3-dioxolane-2,3'-[3H]indole]-1'-propionitrile (68), on reduction with Raney nickel followed by thermal cyclization gave the condensed product(69)[183].

I-3.8) 1,3-Oxathiole

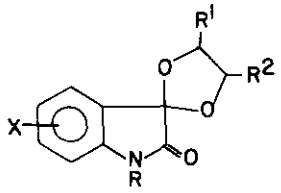
Isatin, on condensation with mercaptodiphenylacetic acid, affords 4',4'-diphenyl-spiro[3H-indole-3,2'-[1,3]oxathiolane]-2,5'(1H)-dione (70) in presence of p-toluenesulphonic acid and desulphurization of the compound has also been carried out[184].

I-3.9) 1,3-Dithiole

Spiro[1,3-dithiolane-2,3'-[3H]indol]-2'(1'H)-one (71) prepared from isatin and 1,2-ethanedithiol has undergone different desulphurization reactions[185].

I-3.10) Pyrimidine

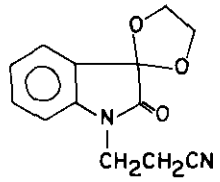
The synthesis of 6'-amino-1-benzyl-3',4'-dihydro-2-oxo-spiro[3H-indole-3,4(3'H)-pyrimidine]-5'-carbonitrile (72) has been reported from 1-benzyl-3-dicyanomethyl-eneindol-2-one and $C_6H_5C(:NH)NH_2.HCl$ in alkaline methanol[186]. 3-Aroylmethylene-indol-2-ones also affords spiro products (73) on reacting with thiourea[94].



(67)

R = H, Me, CD_3, $COCH_3$, CH_2COAr

R', R^2 = H, Me; X = H, F, CF_3



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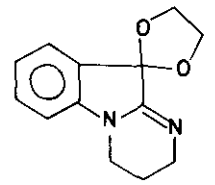
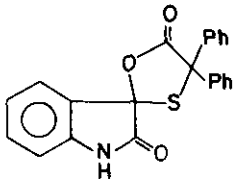


(69)



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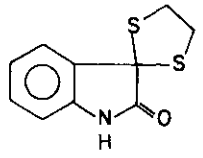
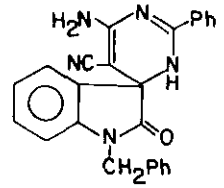
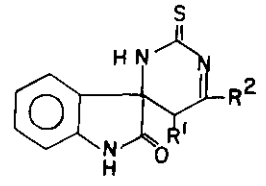


(71)



(72)



(73)

R', R^2 = H, Me, Ph

I-3.11) 1,3-Oxazine

Spiro[3H-indole-3,6'-[6H-1,3]oxazin]-2(1H)-ones (74) are obtained by the catalytic reduction of 3-acetonyloxindole oxime in ethanolic hydrochloric acid over platinum oxide, followed by treatment with ketones[187] and compound (74; R=H, R^1=Me) can also be prepared by cyclocondensation of 3-hydroxy-3-(N-methylaminoethyl)-2-

oxindole with acetaldehyde[188].

I-3.12) 1,3-Dioxine

The synthesis of spiro[1,3-dioxane-2,3'-[3H]indol]-2'(1'H)-ones(75) has recently been reported by us from isatin and 1,3-diols in presence of oxalic acid and compounds can be acylated easily at nitrogen atom[177].

I-3.13) 1,3-Thiazine

Spiro[3H-indole-3,2'-[2H-1,3]thiazin]-2(1H)-ones (76) have been prepared from isatin, 3-mercaptopropylamine hydrochloride and potassium cyanate and are reported to possess antiinflammatory, analgesic and anticonvulsant activities[189].

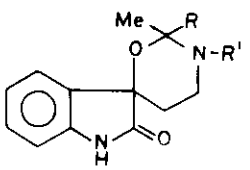
I-3.14) 1,4-Diazepine

Indolyl carbinols (77) have afforded 2,3,5,6-tetrahydrospiro[5H-1,4-diazepine-5,3'-[3H]indol]-2'(1'H)-ones (78) on reacting with ethylenediamine[190,191].

I-4) With Three Heteroatoms

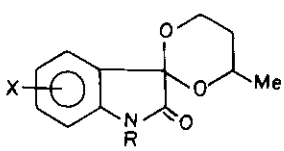
I-4.1) Triazole

Spiro[3H-indole-3,4'-[4H-1,2,3]triazol]-2(1H)-ones (79) are prepared by treating isatin-3-anils with diazomethane in ether at 0°C for 21 days[192].



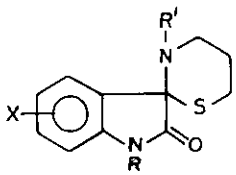
(74)

R = H, Me, Ph
R' = H, Me



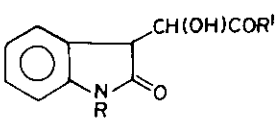
(75)

R = H, $COCH_3$
X = H, F



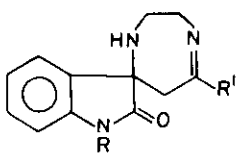
(76)

R = H, Me, Ph, COMe
R' = H, COMe, Carbamoyl
X = H, 5-Cl, 4-Cl, 5,7-diCl, 5-Br, 5-I, 5-F, 5-Me, etc.

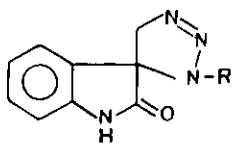


(77)

R = H, Me; R' = Ph, p-tolyl



(78)



(79)

R = aryl, thienyl, 5-bromothienyl, ferrocenyl

I-4.2) Oxadiazole

Spiro[3H-indole-3,5'(2'H)-[1,2,4]oxadiazol]-2(1H)-ones (80) are produced from isatin-3-anils and phenyl cyanate[8].

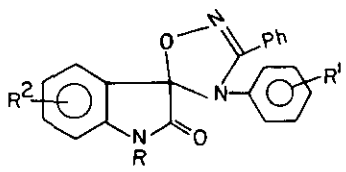
I-4.3) Thiadiazole

The condensation of isatin with phenylthiocarbohydrazide in acetic acid containing conc. hydrochloric acid for 3 h has produced the spiro derivative (81)[193].

The cyclization of isatin-3-thiobenzoylhydrazones also affords spiro[3H-indole-3,2'-[1,3,4]thiadiazol]-2(1H)-ones (82)[194,195].

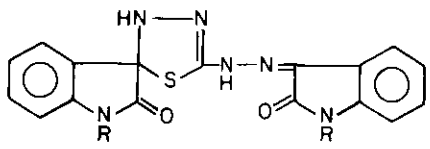
I-4.4) Triazine

The reaction of arylbiguanides (aryl=Ph, 4-MePh, 4-OMePh, 4-ClPh) and N-amidino-o-alkylisoureas with isatin or 1-methylisatin yields 4'-amino-6'-arylamino-spiro[3H-indole-3,2'(1'H)-[1,3,5]triazin]-2(1H)-ones (83) and 6'-alkoxy-4'-amino-spiro[3H-indole-3,2'(1'H)-[1,3,5]triazin]-2(1H)-ones (84), respectively[196].



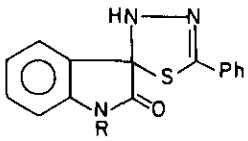
(80)

R = H, Me; R' = H, F, R^2 = H, F, Me, NO_2



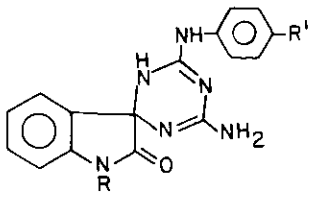
(81)

R = H, Me, pentyl



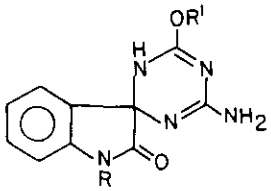
(82)

R = H, Me, Et



(83)

R = H, Me;
R' = H, Me, OMe, Cl



(84)

R = H, Me
R' = alkyl

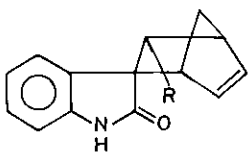
II. TWO RING SYSTEMS

II-1) With No Heteroatom

II-1.1) Bicycloheptane/octane

3-Nitromethylene-2-oxindole with cyclohexa-1,3-diene gives a 4:1 mixture of the adducts, 3-nitro-spiro[bicyclo[2.2.1]hept-5-ene-2,3'-[3H]indol]-2'(1'H)-one (85; R=NO_2) and 3-nitro-spiro[bicyclo[2.2.2]oct-5-ene-2,3'-[3H]indol]-2'(1'H)-one(86;

R=NO_2)[197]. Other 3-substituted methylene-2-oxindoles also produce a mixture of two stereoisomers of (85) and (86) (R=COOMe, COMe, COPh) with cyclopentadiene or cyclohexadiene[198-200]. E-5,7-Dichlorooxindolylidene-chloroacetonitrile affords two isomeric spiro compounds 87 and 88 with cyclopentadiene[201]. Photolysis of 1-methyl-3-diazooxindole in cyclohexene has been reported to produce the spiro-bicycloheptenes[5]. A spiro product (89) is obtained on irradiation of 2,3,3-triphenylindoline in cyclooctene[202].



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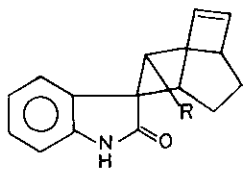
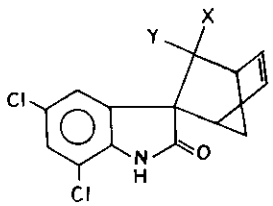
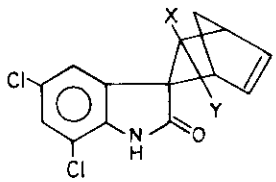


(86)

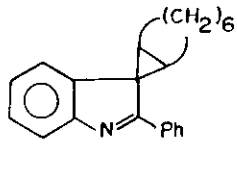


(87)

X= Cl, $CONH_2$; Y=CN,OH



(88)



(89)

II-1.2) Indan

Spiro[indan-2,3'-[3H]indole]-1,2'(1'H)-diones (92) are produced by the cyclization of compounds (90) or (91) with PPA[203,204]. These compounds have also been found to be formed as intermediate during the cyclization of 3-(o-hydroxymethylbenzyl)indole into 1,4-dihydro-2,3-benzocarbazole with phosphorus pentoxide[205].

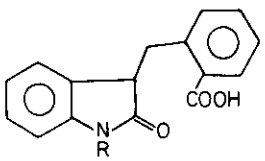
II-1.3) Naphthalene

The cyclization of 3-benzyl-2-oxo-indolin-3-acetic acid (93) with PPA yields 2',3'-dihydro-spiro[3H-indole-3,1'(4'H)-naphthalene]-2,4'(1H)-diones (94)[204].

II-1.4) Tridecamethylene benzene

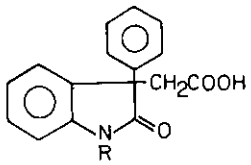
Spiro[3H-indole-3,7'-p-tridecamethylene benzene]-2(1H)-one (95) has been formed by the reaction of p-(7-hydroxy-8-oxotetradecamethylene)benzene with phenyl-

hydrazine[206].



(90)

R = H, Me



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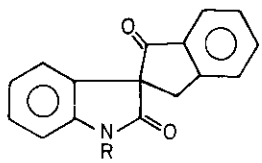

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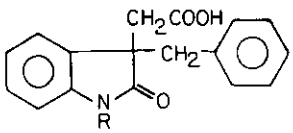
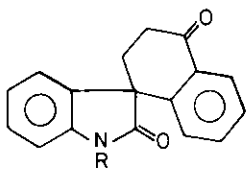
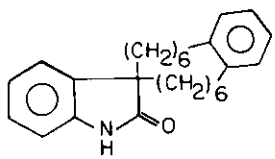


(93)

R = H, Me



(94)



(95)

II-2) With One Heteroatom

II-2.1) Cyclopropane[2,3-c]pyrrole

3-Diazoindole, when heated with N-arylmaleimides, affords corresponding 2'-oxo-N-aryl-spiro[cyclopropane-1,3'-[3H]indole]-2,3-dicarboximide (96)[207].

II-2.2) Indole

Oxindole reacts with o-nitrobenzyl chloride producing 4'-methyl-spiro[2H-indole-2,3'-[3H]indol]-2'-ol (97)[84].

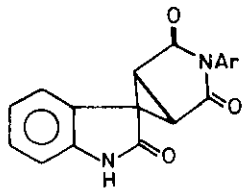
II-2.3) Pyrindene

Irradiation of the indoles (98) in ethanol gives 1,1',2,2',3',7'a-hexahydro-1'-methyl-spiro[3H-indole-3,7'-[7H-1'] pyrindene]-6'-carbonitrile (99)[208]. X-ray crystallographic studies of this compound has also been carried out[209].

II-2.4) Quinoline and Isoquinoline

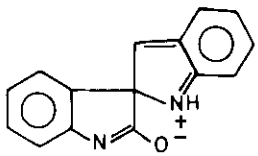
The reaction of 2-(3,4-dimethoxyphenyl)ethylamine with isatin in hydrochloric acid affords 6',7'-dimethoxy-1',2',3',4'-tetrahydro-spiro[3H-indole-3,1'-isoquinolin]-2(1H)-one (100)[210]. 3-Benzyl-3-(2-oxocyclohexyl)-1-methylindol-2-one (101) reacts with primary amines and affords the spiro derivative(102) which is useful as an antiinflammatory drug[211].

Fischer cyclization of quinoline hydrazone (103) with HCl-MeOH has been reported to give a spiro product (104)[212].



(96)

Ar = Ph, o- & p- tolyl



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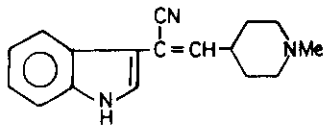

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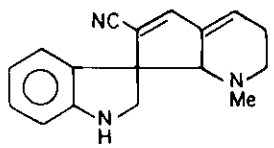

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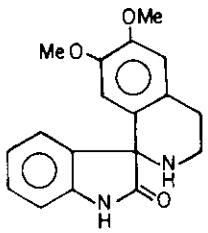

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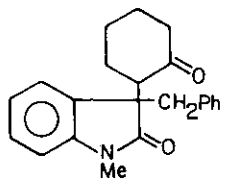

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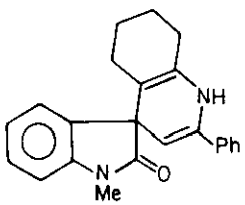
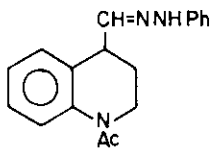
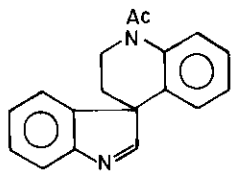


(102)



(103)



(104)

1-Methyl-3-carboethoxy-3-(o-nitrobenzyl)-indol-2-one on reduction with Pd/C also affords spiro quinolines[213].

II-2.5) Pyrrolizine

Spiro [3H-indole-3,1'-[1H]pyrrolizine] derivatives (105; R=Me, n=3) have been prepared by the reaction of chlorobutraldehyde with 2-hydroxytryptamine hydrochloride[214,215].

The reaction of condensed indole derivatives (106) with sodium/ethanol affords 2',3'-dihydro-7'-(1-pyrrolidinyl)-spiro [3H-indole-3,1'-[1H]pyrrolizine]-2,5'(1H,7'H)-diones (107) which are useful as inflammation inhibitors and uterus stimulators[216,217].

II-2.6) Indolizine

Spiro[3H-indol-3,1'(5'H)-indolizine]derivatives (105; n=4) have been obtained by various reactions, viz:

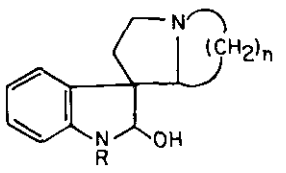
(i) By the reaction of 5-chlorovaleraldehyde with 2-hydroxytryptamine hydrochloride (105; R=H, n=4)[214,215].

(ii) Hydrogenation of 3-(2-piperidylmethylene)-2-oxindole followed by treatment with formaldehyde (105; R=H, n=4)[218].

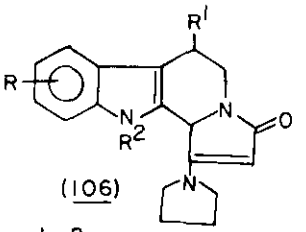
(iii) The treatment of p-nitrophenyl-3-indole acetate with $H_2N(CH_2)_4CH(OEt)_2$ followed by hydrolysis and cyclization with sodium hydroxide(105; R=CHO, n=4)[219].

The indoline derivative (108) has been produced by treating β,β'-disubstituted oxindoles with Et_3OBF_4 followed by neutralization with aqueous K_2CO_3[220].

The spiro compounds 110 and 111 are obtained from condensed indole derivatives (109) on treatment with acetic acid, potassium hydroxide and methanol[221].

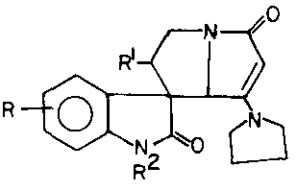


(105)

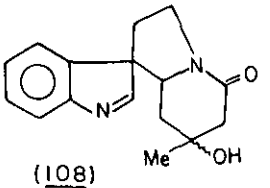


(106)

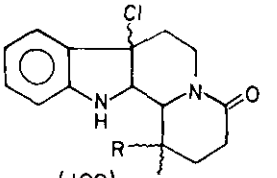
R,R',R²=H,H,Et; H,Me, Me; 7-Me,H,Me; 5-OMe,H,Me



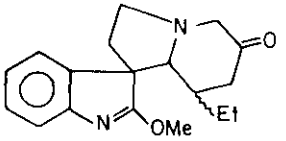
(107)



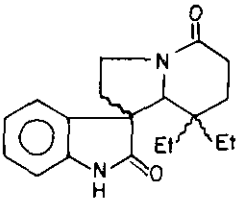
(108)



(109) R = H, Et



(110)



(111)

The oxidation of 3-oxotabursonine with potassium permanganate afforded a similar compound[222].

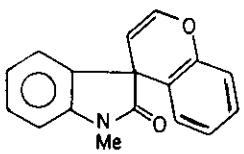
Mass spectral fragmentations of the compounds have also been described[223].

II-2.7) Benzopyran

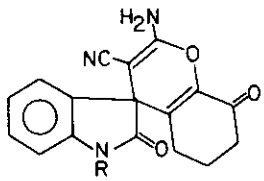
1-Methyl-3-(2-oxocyclohexyl)-3-phenacyloxindole, when refluxed in methanolic HCl, affords spiro[4H-benzopyran-4,3'-[3H]indol]-2'(1'H)-one (112) which displayed antiinflammatory action[141]. 3-Dicyanomethyleneindol-2-one, with 1,3-cyclohexane dione, gives the spiro product (113)[154].

II-2.8) Thiochroman

Benzothiepinoindoles (114) on treatment with HCl, give spiro[3H-indole-3,4'-thiochroman]-2(1H)-ones (115). The former compounds are obtained from 5-oxo-2,3,4,5-tetrahydrobenzo[b]thiepin and phenylhydrazine hydrochloride. The

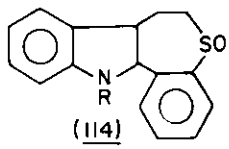


(112)



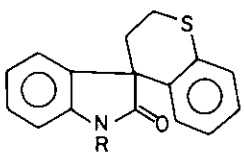
(113)

R=H, Me

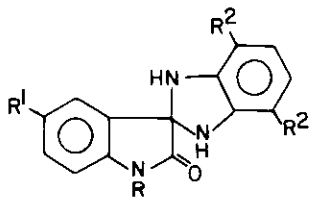


(114)

R=CH_2CH_2CN, CH_2CH_2COOH, CH_2CH_2COOEt



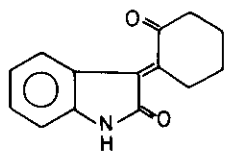
(115)



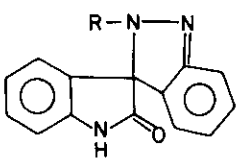
(116)

R=H, Ac, Me; R^1=H, NO_2

R^2=1,4-dibutoxy, 1,4-heptyloxy

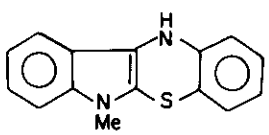


(117)

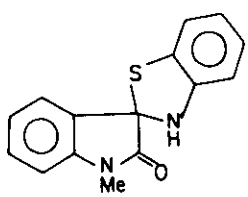


(118)

R=H, Ph



(119)



(120)

compounds have been used to inhibit the gastric acid secretion in rats[224-227].

II-3) With Two Heteroatoms

II-3.1) Benzimidazole

1,3-Dihydro-spiro[2H-benzimidazole-2,3'-[3H]indol]-2'(1'H)-ones (116) have been prepared by refluxing the corresponding 1,2-phenylenediamine with appropriate indole-2,3-dione[228-230].

Polymers of these compounds are obtained when polycondensation of biisatyls is carried out with aromatic tetramines in polar organic solvents[231].

II-3.2) Benzpyrazole

The cyclocondensation of hydrazine derivatives with 3-alkyleneindol-2-one (117) affords 5,6,7,8-tetrahydro-spiro[benzpyrazole-3,3'-[3H]indol]-2'(1'H)-ones (118)[94].

II-3.3) Benzothiazole

Jackson et al. have reported the air oxidation of indolobenzothiazine (119) into 1'-methyl-spiro[benzothiazole-2(3H), 3'-[3H]indol]-2'(1'H)-one(120) in ethanol[232].

II-3.4) Quinazoline

The spiro structure (121) was assigned to isamic acid obtained by the reaction of isatin with ammonia which has been confirmed by various spectral studies[233,234]. Quinazoline carboxamides (122) on thermal cyclization have afforded spiro[3H-indole-3,4'(1'H)-quinazoline]-2,2'(1H,3'H)-diones (123)[235].

II-3.5) Quinoxaline

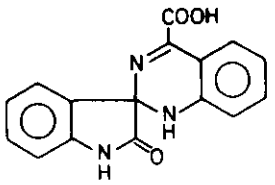
Quinoxaline carboxanilides (124) isomerize to spiro[3H-indole-3,2'(3'H)-quinoxaline]-2,3'(1H)-diones (125; R=same or different Cl, H, MeO, Me; R^1=H, Ac, Me; R^2=Me, H) in the presence of concentrated sulphuric acid at 0°C or hot ethanolic hydrochloric acid. If R^2 is an electron withdrawing group, the reaction does not take place with sulphuric acid[236-240].

II-3.6) Benzoxazine

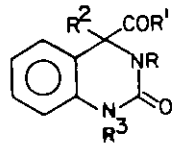
Diebold and Wolf refluxed isatin with o-$NH_2C_6H_4CH(OH)Ph$ in xylene in presence of zinc chloride to obtain 6-chloro-1,4-dihydro-4-phenyl-spiro[2H-3,1-benzoxazine-2,3'-[3H]indol]-2'(1'H)-one (126) which has been found to possess bactericidal and CNS depressant activity[241].

II-3.7) Benzodiazepine

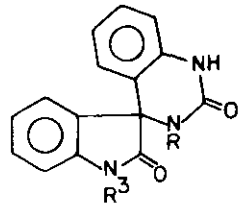
Indolyl carbinols afford spiro[2H-1,5-benzodiazepine-2,3'-[3H]indole]derivatives (127) on treatment with 1,2-phenylenediamines[190,191].



(121)

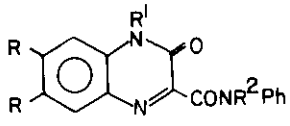


(122)

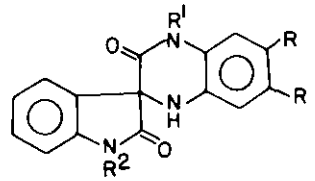


(123)

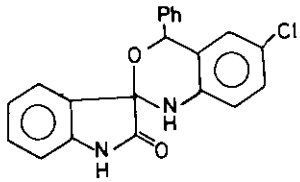
R=Me, Ph; R^1=NHPh, NHNHBz;
R^2=OH; R^3=H, Me



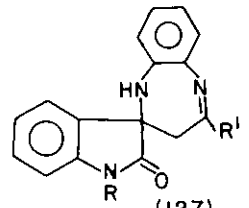
(124)



(125)



(126)



(127)

R=H, Me
R^1=Ph, p-tolyl

II-4) With Three and More Than Three Heteroatoms

II-4.1) Imidazo[4,5-b]pyridine

The condensation of 1,2-diaminopyridine with isatin and N-acetylisatin yields 1,3-dihydro-spiro[2H-imidazo[4,5-b]pyridine-2,3'-[3H]indol]-2'(1'H)-ones(128)[242].

II-4.2) Pyrano[2,3-c]pyrazole

Spiro[3H-indole-3,4'(1'H)-pyrano[2,3-c]pyrazoles](129) are produced from 3-dicyanomethylene-2-oxindole and 3-methyl-1-phenyl-5-pyrazolone[154].

II-4.3) Pyrano[2,3-d]pyrimidine

3-Dicyanomethylene-2-oxindole, when treated with barbituric acid, forms 7'-amino-1,1',2,2',3',4'-hexahydro-2,2',4'-trioxo-spiro[3H-indole-3,5'-[5H]pyrano[2,3-d]pyrimidine]-6'-carbonitrile (130)[154].

II-4.4) Imidazo[4,5-d]pyrimidine

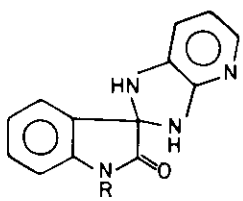
Isatin and 4,5-diaminopyrimidine produce 1,3-dihydro-spiro[2H-imidazo[4,5-d]pyrimidine-2,3'-[3H]indol]-2'(1'H)-ones (131)[242].

III. THREE RING SYSTEMS

III-1) With No Heteroatom

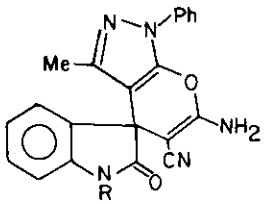
III-1.1) Fluorene

Rapoport et al.[243] have synthesized spiro[fluorene-9,3'-[3H]indol]-2'(1'H)-one (132) by the reaction of 9-(o-ethoxycarbonylaminophenyl)fluorene with sodium and 9-(o-azidocarbonylphenyl)fluorene with KOH. The synthesis of 2-phenyl-spiro[fluorene-9,3'-indoline] (133) has been reported by Bavin[244] through the cyclization of 9-benzoylfluorene with phenylhydrazine.



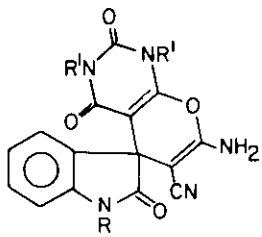
(128)

R = H, $COCH_3$



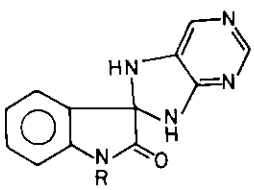
(129)

R = H, Me



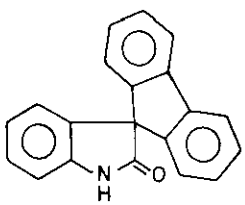
(130)

R, R' = H, Me

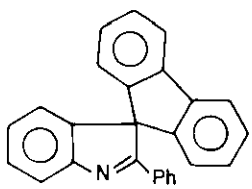


(131)

R = H, $COCH_3$



(132)



(133)

III-2) With One Heteroatom

III-2.1) Cyclopenta[2,3-b]indole

Michael addition of indoles to 2-oxindolin-3-ylidene ketones results in the formation of spiro[cyclopenta[2,3-b]indole-1,3'-[3H]indol]-2'(1'H)-one derivatives (134 and 135) as minor products[245].

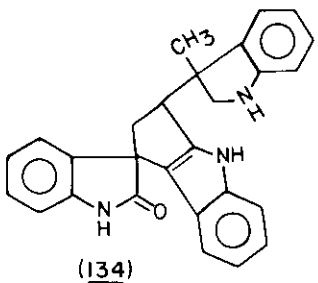
III-2.2) Iminoethanoindan

The treatment of compound (136) with methanolic potassium hydroxide has given

rise to 4,5,6,7-tetrahydro-10-methyl-spiro[3aH-3,7a-iminoethanoindan-1,3'-indole] (137)[246-248].

III-2.3) Pyrrolo[1,2-c]isoquinoline

The reaction of 2-oxoindolylethylamine hydrochloride with 3,4-dimethoxyphenylacetaldehyde gave spiro[3H-indole-3,1'-pyrrolo[1,2-c]isoquinoline] derivative (138)[97].



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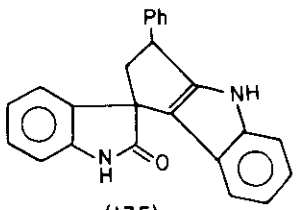
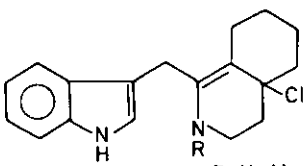
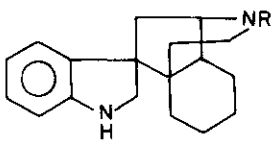


(135)



(136) R=H, Me



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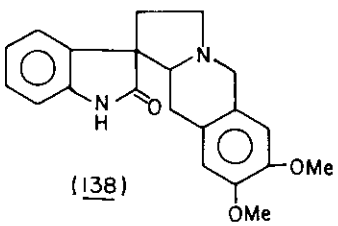
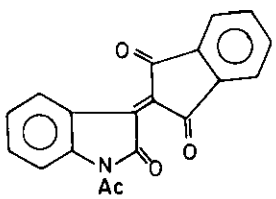
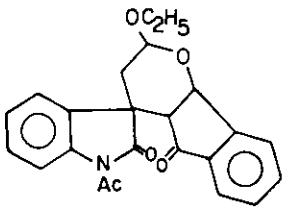


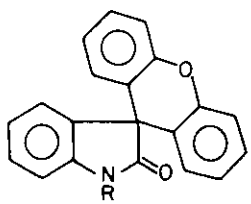
(138)



(139)



(140)



R=H, Me

(141)

III-2.4) Indeno[1,2-b]pyran

1'-Acetyl-2-ethoxy-2,3-dihydro-spiro[indeno[1,2-b]pyran-4(5H),3'-[3H]indole]-2',5(1'H)-dione (140) is obtained when compound (139) is treated with $EtOCH{=}CH_2$[249].

III-2.5) Xanthene

The condensation of isatin with phenol or cresol at 200-240°C or in the presence of sulphuric acid at 80°C gives spiro[3H-indole-3,9'-[9H]xanthene] derivatives (141)[250-252]. 1,3-Cyclohexanedione derivatives also condense in the same way yielding 3',4',6',7'-tetrahydro-spiro[3H-indole-3,9'-[9H]xanthene]-1',2,8'(1H,2'H,5'H)-trione[253].

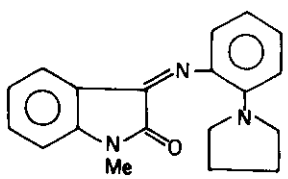
III-3) With Two Heteroatoms

III-3.1) Pyrrolo[1,2-a]quinoxaline

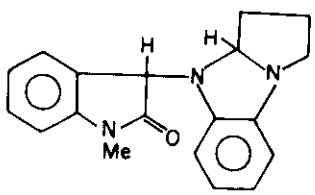
Tetrahydro-spiro[3H-indole-3,4'(5'H)-pyrrolo[1,2-a]quinoxalin]-2(1H)-one (144) is obtained by the treatment of either anil (142) or tetrahydropyrrole[1,2-a]benzimidazole (143) with acid or ethanol[254,255].

III-3.2) Pyrrolo[1,2-a][1,4]benzodiazepine

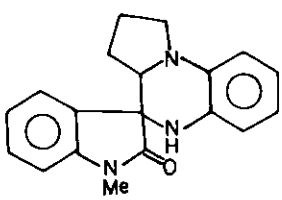
The cyclization of N-(o-aminomethylphenyl)pyrrole hydrochloride with isatin in DMF affords 5,6-dihydro-spiro[3H-indol-3,4'-[4H]pyrrolo[1,2-a][1,4]benzodiazepin]-2(1H)-one (146)[256].



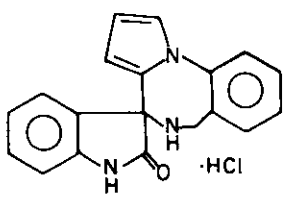
(142)



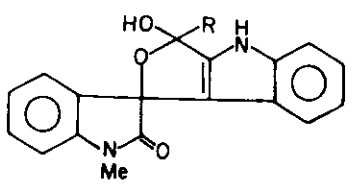
(143)



(144)



(145)



(146)

R = Me, Ph

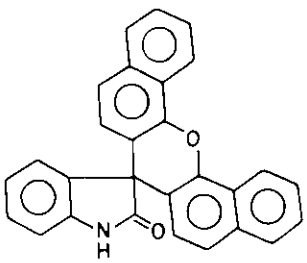
III-3.3) Furo[3,4-b]indole

Spiro[furo[3,4-b]indole-1,3'-[3H]indol]-2'(1'H)-ones (146) have been obtained on heating 1-methyl-3-(3-indolyl)-dioxindole with acetic anhydride-acetic acid[257].

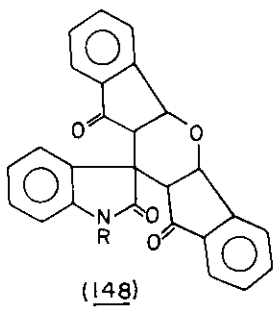
MISCELLANEOUS

The condensation of isatin with α-naphthol gave the spiro product (147)[250,258] and with indan-1,3-dione in 1:2 ratio (148) was obtained which on refluxing with ammonium acetate or aniline gave (149)[259].

The reaction product of isatin with acetic anhydride and pyridine has been shown to be (150)[260].

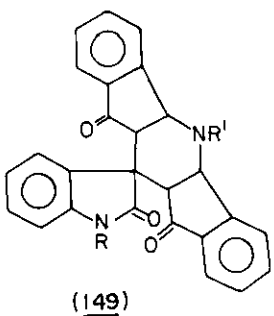


(147)



(148)

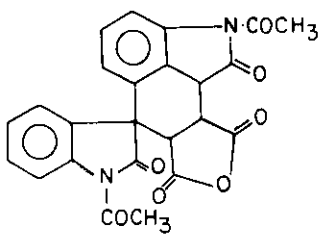
R = H, $COCH_3$



(149)

R = H, $COCH_3$

R' = H, Ph



(150)

Oxindolylidene-acetone has been shown to react with a variety of acetylenic dienophiles to yield various derivatives of naphthostyrils[261].

REFERENCES

1. J.M. Muchowski, D.E. Horning and G. Lacasse, Canad. J. Chem., 1971, 49, 246.
2. E. Wenkert and E.C. Blossey, J. Org. Chem., 1962, 27, 4656.
3. M. Makosza and M. Fedorynski, Rocz. Chem., 1971, 45(11), 1861; Chem. Abstr., 1972, 76, 113013u.
4. J.E. Johansen, B.D. Christie and H. Rapoport, J. Org. Chem., 1981, 46, 4914.
5. E.J. Moriconi and J.J. Murray, J. Org. Chem., 1964, 29, 3577.
6. H. Otomasu, T. Tanaka and M. Aoyagi, Chem. & Pharm. Bull., 1976, 24, 782.
7. W.D. Closson, S.A. Roman, G.J. Kwiatkowski and D.A. Corwin, Tetrahedron Lett., 1966, 2271.
8. F. Albrecht, Justus Liebigs Ann. Chem., 1978, 717, Chem. Abstr., 1978, 89, 108935k.
9. M. Chiericato, P. Dalla Croce and E. Licandro, J. Chem. Soc., Perkin Trans. 1, 1979, 211.
10. A. Remers and M.J. Weiss, Tetrahedron Lett., 1968, 81.
11. E. Wenkert and T.L. Reid, Chem. & Ind., 1953, 1390.
12. M. Kawada, Y. Kawano, H. Sugihara, S. Takei and I. Imada, Chem. & Pharm. Bull., 1981, 29, 1900.
13. T. Nozoye, Ann. Rept. ITSUU Lab No. 8, 1957, 12-14; Chem. Abstr., 1957, 51, 15273gh.
14. D.G. Markes and A. Burger, J. Amer. Chem. Soc., 1949, 71, 2031.
15. M. Ohkawa and I. Koichi, Japan. Kokai, 1974, 74 75,646; Chem. Abstr., 1975, 82, 59915y.
16. M. Ohkawa and I. Koichi, Japan.Kokai, 1974, 74 99,128; Chem. Abstr., 1975, 83, 181111u.
17. K. Eiter, Experientia, 1955, 11, 189; Chem. Abstr., 1956, 50, 4908d.
18. G. Tacconi, F. Marinone and G. Desimoni, Gazz. Chim. Ital., 1970, 100, 284; Chem. Abstr., 1970, 73, 25334g.
19. G. Tacconi, A. Gamba, F. Marinone and G. Desimoni, Tetrahedron, 1977, 27, 561.
20. G. Tacconi, A.G. Invernizzi and G. Desimoni, J. Chem. Soc., Perkin Trans. 1, 1976, 1872.
21. J.A. Ballantine, J. Chem. Soc., Perkin Trans.1, 1979, 1182.
22. J.A. Ballantine, M. Alam and G.W. Fishlock, J. Chem. Soc., Perkin Trans. 1, 1977, 1781.
23. S.G.P. Plant and R. Robinson, Nature, 1950, 165, 36; Chem. Abstr., 1950, 44, 4461.

24. J.B. Patrick and B. Witkop, J. Amer. Chem. Soc., 1950, 72, 633.

25. A.H. Jackson, B. Naidoo, A.E. Smith, A.S. Bailey and M.H. Vandrevala, J. Chem. Soc., Chem. Commun., 1978, 779.

26. R.F. Moore and S.G.P. Plant, J. Chem. Soc., 1951, 3475.

27. A.G. Shultz and Chin-Keng She, Tetrahedron, 1980, 36, 1757.

28. N.A. Jonsson and P. Moses, Acta Chem. Scand., Ser. B, 1974, 28, 225; Chem. Abstr., 1974, 80, 145946z.

29. N.A. Jonsson and P. Moses, ibid., 1974, 28, 441; Chem. Abstr., 1974, 81, 63012y.

30. N.A. Jonsson and P. Moses, Swed. Patent, 1974, 366,309; Chem. Abstr., 1975, 83, 79076z.

31. G. Winters and N. Di. Mola, Ger. Patent, 1975, 2,442,667; Chem. Abstr., 1975, 83, 28096y.

32. Y. Kanaoka, K. Miyashita and O. Yonemitsu, Tetrahedron, 1969, 25, 2757.

33. B. Witkop and J.B. Patrick, J. Amer. Chem. Soc., 1951, 73, 2188.

34. E.E. Van Tamelen, K.V. Siebrasse and J.B. Hester, Chem. & Ind., 1956, 1145.

35. A.S. Bailey, R. Scattergood and W.A. Warr, J. Chem. Soc. C, 1971, 2479.

36. A.S. Bailey, A.J. Buckley and J.F. Seager, J. Chem. Soc., Perkin Trans. 1, 1973, 1809.

37. R. Iyer, A.H. Jackson and P.V.R. Shannon, J. Chem. Soc., Perkin Trans. 2, 1973, 878.

38. G.A. Bahadur, A.S. Bailey and P.A. Baldry, J. Chem. Soc., Perkin Trans. 1, 1977, 1619.

39. G.A. Bahadur, A.S. Bailey, G. Costello and P.W. Scott, ibid., 1979, 2154.

40. B. Witkop and J.B. Patrick, J. Amer. Chem. Soc., 1951, 73, 1558.

41. C.A. Dimeroon and L.G. Humber, U.S.Patent, 1980, 4,226,860; Chem. Abstr., 1981, 94, 15598r.

42. M.E. Kuehne and R. Hafter, J. Org. Chem., 1978, 43, 3702.

43. R.J. Owellen, ibid., 1974, 39, 69.

44. Y. Kikugawa, Y. Miyaki and M. Kawase, Chem. & Pharm. Bull., 1981, 29, 1231.

45. V.E. Golubev and N.N. Suvorov, Khim. Geterotsikl. Soedin., 1970, 759; Chem. Abstr., 1970, 73, 109619s.

46. A.H. Jackson and B. Naidoo, J. Chem. Soc., Perkin Trans. 2, 1973, 548.

47. A. Kubo, T. Nakai, T. Nozoye, A. Itai and Y. Iitaka, Heterocycles, 1978, 9, 1051.

48. B. Witkop and J.B. Patrick, J. Amer. Chem. Soc., 1953, 75, 2572.

49. M. Nakazaki, Bull. Chem. Soc. Jpn., 1960, 33, 472.

50. S. Isoe and M. Nakazaki, Chem. & Ind., 1959, 1574.

51. Y. Kanaoka, K. Miyashita and O. Yonemitsu, Chem. & Pharm. Bull., 1970, 18, 634.

52. I.J. Tickle and C.K. Prout, J. Chem. Soc. C, 1971, 3401.

53. A. Itai, Y. Iitaka and A. Kubo, Acta Crystallogr., Sect. B., 1978, B34, 3775.

54. D.J. Watkin, M.R. Sims and M.C. Couldwell, Cryst. Struct. Commun., 1979, 8, 463; Chem. Abstr., 1979, 91, 47731h.

55. N.A. Jonsson, L. Mikiver and P. Moses, Ger. Patent, 1973, 2,245,159; Chem. Abstr., 1973, 78, 159460g.

56. M. Wolf and A.A. Mascitti, U.S. Patent, 1968, 3,395,156; Chem. Abstr., 1968, 69, 96504r.

57. R.E. Lyle and L. Skarlos, Chem. Commun., 1966, 644.

58. G. Palazzo and V. Rosnati, Gazz. Chim. Ital., 1953, 83, 211.

59. A.S. Kende and J.C. Hodges, Synth. Comm., 1982, 12, 1; Chem. Abstr., 1982, 96, 181097w.

60. K. Okada, H. Sakuma, M. Kondo and S. Inoue, Chem. Lett., 1979, 213.

61. M.S. Gibson, J. Chem. Soc., 1961, 2249.

62. B. Zeeh, Angew. Chem. Int. Ed. Engl., 1967, 6, 453; Chem. Abstr., 1967, 67, 43623f.

63. B. Zeeh, Chem. Ber., 1968, 101, 1753.

64. B. Zeeh, Chem. Ber., 1969, 102, 1876.

65. A.N. Kost, G.A. Golubeva, V.G. Zabrodnyaya and Yu. N. Portnov, Khim. Getereotsikl. Soedin., 1975, 1632; Chem. Abstr., 1976, 84, 105529s.

66. G. Tacconi, F. Marinone, A. Gamba and G. Desimoni, Tetrahedron, 1972, 28, 1517.

67. A.S. Bailey and J.F. Seager, J. Chem. Soc., Perkin Trans. 1, 1974, 763.

68. A.S. Bailey and P.A. Wilkinson, J. Chem. Soc., Perkin Trans. 1, 1976, 481.

69. Rohm and Haas Co., Brit. Patent, 1962, 913,937; Chem. Abstr., 1963, 59, 577f.

70. Rohm and Haas Co., Brit. Patent, 1961, 913,931; Chem. Abstr., 1963, 59, 1596g,h.

71. Rohm and Haas Co., Brit. Patent, 1962, 913,932; Chem. Abstr., 1963, 59, 1597d.

72. D.D. Chapman and L.G.S. Brooker, U.S. Patent, 1972, 3,649,266; Chem. Abstr., 1972, 76, 147257s.

73. K.G. Dzhaparidze, D.P. Maisuradze, G.G. Gachechiladze and E.S. Gomelauri, Khim. Getereotsikl. Soedin., 1971, 7, 775.

74. W.N. Ross, B.M. Salzberg, L.B. Cohen, A. Grinvald, H.V. Davila, A.S. Waggoner and C.H. Wang, J. Membr. Biol., 1977, 33, 141.

75. F. Arndt, B. Eistert and W. Ender, Ber., 1929, 62B, 44.

76. A. Schoenberg and K. Junghans, Ber., 1963, 96, 3328.

77. W.C. Anthony, J. Org. Chem., 1966, 31, 77.

78. Upjohn Co., French Patent, 1966, 1,445,824; Chem. Abstr., 1967, 66, 75921x.

79. J.W. Ager, F.A. Eastwood and R. Robinson, Tetrahedron Supp. No. 7, 1966, 277.

80. Upjohn Co., Netherland Appl., 1966, 6,505,845; Chem. Abstr., 1967, 67, 21850e.

81. W.C. Anthony, U.S. Patent, 1968, 3,413,299; Chem. Abstr., 1969, 70, 47294j.

82. G. Kobayashi, S. Furukawa and Y. Matsuda, Yakugaku Zasshi, 1966, 86, 1156; Chem. Abstr., 1967, 67, 3032f & 108594u.

83. T. Teshigawara, G. Kobayashi and Y. Matsuda, Japan Patent, 1967, 15542; Chem. Abstr., 1968, 69, 2877q.

84. R. Kikumoto and T. Kobayashi, Tetrahedron, 1966, 22, 3337.

85. J.T. Baker and M.D. Sutherland, Tetrahedron Lett., 1968, 43.

86. J.T. Baker and C.C. Duke, Aust. J. Chem., 1976, 29, 1023.

87. P. Bravo, G. Gaudiano and A. Umani-Ronchi, Gazz. Chim. Ital., 1970, 100, 652.

88. G. Kobayashi and Y. Matsuda, Japan Patent, 1968, 68,03,385; Chem. Abstr., 1968, 69, 96716m.

89. K. Kikugawa and M. Ichino, Chem. & Pharm. Bull., 1973, 21, 1151.

90. K.M. Hassan, A.K. El-Shafei and H.S. El-Kaehef, Z. Naturforsch., B. Anorg. Chem., Org. Chem., 1978, 33B, 1508; Chem. Abstr., 1979, 90, 121763t.

91. K.M. Hassan, A.K. El-Shafei and H.S. El-Kaehef, ibid., 1978, 33B, 1515; Chem. Abstr., 1979, 90, 121474z.

92. K.M. Hassan and Z.H. Khalil, ibid., 1979, 34B, 621; Chem. Abstr., 1979, 91, 56891n.

93. K.M. Hassan and Z.H. Khalil, ibid., 1979, 34B, 1326; Chem. Abstr., 1980, 92, 146666t.

94. K.M. Hassan and Z.H. Khalil, J. Prakt. Chem., 1979, 321, 870.

95. F.M. Atta, M.S.K. Youssef and K.M. Hassan, Indian J. Chem. Sect. B, 1979, 18B, 475.

96. T.H. Koch, J. Olesen and J. Foy, J. Org. Chem., 1975, 40, 117.

97. Y. Ban and T. Oishi, Chem. & Ind., 1960, 349.

98. A.B.A. Jansen and C.G. Richardo, Tetrahedron, 1965, 21, 1327.

99. J. Harley-Mason and R.F.J. Ingleby, J. Chem. Soc., 1958, 3639.

100. M.J. Kornet and A.P. Thio, J. Med. Chem., 1976, 19, 892.

101. J.A. Weisbach, U.S. Patent, 1967, 3,299,075; Chem. Abstr., 1967, 67, 32605a.

102. M. Seto, T. Oishi, M. Mitsuhashi and Y. Ban, Chem. & Pharm. Bull., 1976, 24, 1393.

103. T. Oishi, M. Nagai and Y. Ban, Tetrahedron Lett., 1968, 491.

104. J.R. Williams and L.R. Unger, J. Chem. Soc. D, 1970, 1605.

105. K. Blau, G.S. King and M. Sandler, Biomed. Mass Spectrom., 1977, 4, 232; Chem. Abstr., 1978, 88, 136439z.

106. K. Curness and S. Dyke, Heterocycles, 1979, 12, 1133.

107. R.C. Elderfield and H.H. Rembges, J. Org. Chem., 1967, 32, 3809.

108. H. Schaefer, Arch. Pharm., 1970, 303, 183.

109. F.M. Hershenson, K.A. Prodan, R.L. Kochman, J.L. Bloss and C.R. Mackeru, J. Med. Chem., 1977, 20, 1448.

110. F.M. Hershenson, L. Swenton and K.A. Prodan, Tetrahedron Lett., 1980, 21, 2167.

111. J.A. Weisbach, E. Macko, N.J. De Sanctis, M.P. Cava and B. Douglas, J. Med. Chem., 1964, 7, 735.

112. A.S. Bailey, C.M. Birch, D. Illingworth and J.C. Willmott, J. Chem. Soc., Perkin Trans. 1, 1978, 1471.

113. A.S. Bailey and M.H. Vandrevala, J. Chem. Soc., Perkin Trans. 1, 1980, 1512.

114. S. Beveridge and J.L. Huppatz, Aust. J. Chem., 1970, 23, 781.

115. S. Beveridge and J.L. Huppatz, Aust. J. Chem., 1972, 25, 1341.

116. A.H. Jackson and A.E. Smith, Tetrahedron, 1968, 24, 403.

117. M. Mori and Y. Ban, Heterocycles, 1978, 9, 391.

118. W.N. Speckamp, S.J. Veenstra, J. Dijkink and R. Fortgens, J. Amer. Chem. Soc., 1981, 103, 4643.

119. S.J. Veenstra and W.N. Speckamp, J. Amer. Chem. Soc., 1981, 103, 4645.

120. H. Von Dobeneck, E. Erunner, H. Bunke, G. Metzner, R. Schmidt, E. Weil and J. Sonnenbichler, Liebigs Ann. Chem., 1981, 410.

121. T. Hino, H. Miura, T. Nakamura, R. Murata and M. Nakagawa, Heterocycles, 1975, 3, 805.

122. T. Hino, H. Miura, R. Murata and M. Nakagawa, Chem. & Pharm. Bull., 1978, 26, 3695.

123. E.C. Kendall and A.E. Osterberg, J. Amer. Chem. Soc., 1927, 49, 2047.

124. A. Patchornik, W.B. Lawson and B. Witkop, ibid., 1958, 80, 4748.

125. T. Ohnuma, H. Kasuya, Y. Kimura and Y. Ban, Heterocycles, 1982, 17 (Special issue), 377.

126. A. Fontana, F.M. Veronese and E. Boccu, Acta Vitaminol. Enzymol., 1975, 29, 270.

127. G.S. Ketrupha, A.B. Silaev and S.N. Maeushkaya, Khim. Prir. Soedin., 1977, 431.

128. G. Stochrer, J. Heterocycl. Chem., 1976, 13, 157.

129. T. Nagasaka and S. Ohki, Chem. & Pharm. Bull., 1971, 19, 603.

130. W.E. Savige and A. Fontana, Semisynth. Pept. Proteins, Pap. Int. Meet. Protein Semisynth., 1977, 381.

131. R.L. Hinman and C.P. Bauman, J. Org. Chem., 1964, 29, 1206.

132. S. Oki and T. Nagasaka, Japan. Kokai, 1973, 73 14,665; Chem. Abstr., 1973, 78, 147830q.

133. N.D. Heindel and J.A. Minatelli, J. Pharm. Sci., 1981, 70, 84.

134. R.G. Amiet, F.W. Eastwood and I.D. Rae, J. Chem. Soc. D, 1971, 1614.

135. R.G. Amiet, F.W. Eastwood and I.D. Rae, Aust. J. Chem., 1972, 25, 1473.

136. S. Oki and T. Nagasaka, Japan. Kokai, 1973, 73 14,666; Chem. Abstr., 1973, 78, 136258h.

137. G. Kobayashi, Y. Tominaga, S. Kisaki, M. Sone and S. Ueno, Chem. & Pharm. Bull., 1973, 21, 2344.

138. A.S. Bailey, P.A. Hill and J.F. Seager, J. Chem. Soc., Perkin Trans. 1, 1974, 967.

139. J. Bergman, S. Abrahamsson and B. Dahlen, Tetrahedron, 1971, 27, 6143.

140. E. Kretz, J.M. Muller and E. Schlitter, Helv. Chim. Acta, 1952, 35, 520.

141. G. Kobayashi and Y. Matsuda, Japan Patent, 1970, 70 25,894; Chem. Abstr., 1971, 74, 3529t.

142. K. Ono, K. Sasajima, T.J. Katsube and H. Yamamoto, Japan. Kokai, 1978, 78 68,784; Chem. Abstr., 1978, 89, 129425j.

143. Sumitomo Chemical Co., Ltd., Belg. Patent, 1978, 867,517; Chem. Abstr., 1979, 90, 121443p.

144. C.J. Cavalleto and A.P. Gray, U.S. Patent, 1968, 3,409,626; Chem. Abstr., 1969, 70, 47306q.

145. Hoechst A.-G., Japan Kokai Tokkyo Koho, 1978, 78 132,578; Chem. Abstr., 1979, 90, 137699n.

146. H.H. Ong and J.A. Profitt, U.S. Patent, 1980, 4,209,625; Chem. Abstr., 1980, 93, 204474n.

147. H.H. Ong and M.N. Agnew, J. Heterocycl. Chem., 1981, 18, 815.

148. H.H. Ong and J.A. Profitt, U.S. Patent, 1981, 4,307,235; Chem. Abstr., 1982, 96, 122653t.

149. K. Higashiyama and H. Otomasu, Chem. & Pharm. Bull., 1980, 28, 1540.

150. T. Naito, O. Miyata and I. Ninomiya, Fukuoka Kagaku Toronkai Koen Yoshishu, 12th, 1979, 126; Chem. Abstr., 1980, 93, 95470h.

151. T. Naito and I. Ninomiya, Heterocycles, 1981, 15, 735.

152. N. Irwin and Co., Brit. Patent, 1960, 842,995; Chem. Abstr., 1961, 55, 7439b.

153. M.J. Kornet, A.P. Thio and J.H. Thorstenson, J. Pharm. Sci., 1977, 66, 1022.

154. K. Higashiyama and H. Otomasu, Chem. & Pharm. Bull., 1980, 28, 648.

155. K. Ninomiya, Jpn. Kokai Tokkyo Koho, 1980, 80 164,683; Chem. Abstr., 1981, 95, 25036r.

156. E. Voigt and H. Meier, Agnew. Chem., 1975, 87, 109.

157. E. Voigt and H. Meier, Chem. Ber., 1975, 108, 3326.

158. H.G. Aurich and U. Grigo, Chem. Ber., 1976, 109, 200.

159. A.M. El-Abbady, M.A. Omara and N.G. Khandil, Rev. Roum. Chim., 1974, 19, 79.

160. G.I. Zhungietu, G.A. Dragalina and G.N. Dorofeenko, Khim. Getereotsikl. Soedin., 1973, 40; Chem. Abstr., 1973, 78, 111201w.

161. G.B. Bennett, R.B. Mason, M.J. Shapiro and J. Michael, J. Org. Chem., 1978, 43, 4383.

162. H. Otomasu, K. Natori and H. Takahashi, Chem. & Pharm. Bull., 1975, 23, 1431.

163. H. Otomasu and S. Omiya, Japan Kokai, 1975, 75 137,979; Chem. Abstr., 1976, 85, 21357s.

164. D.R. Brittain and R. Wood, Eur. Pat. Appl., 1981, 28,906; Chem. Abstr., 1981, 95, 150660r.

165. J.W. Clark-Lewis and J.A. Edgar, J. Chem. Soc., 1965, 5551.

166. G. Kobayashi and Y. Matsuda, Japan Patent, 1970, 70 40,894; Chem. Abstr., 1971, 75, 20386g.

167. G. Tacconi, P.P. Righetti and G. Desimoni, J. Prakt. Chem., 1980, 322, 679.

168. A. Umehara and H. Sato, J. Polym. Sci., Polym. Chem. Ed., 1978, 16, 2039; Chem. Abstr., 1979, 90, 23767c.

169. H. Otomasu and S. Ohmiya, Japan Kokai, 1975, 75 140,441; Chem. Abstr., 1976, 85, 32991v.

170. K.C. Joshi, R. Patni and P. Chand, Heterocycles, 1981, 16, 1555.

171. K.C. Joshi, R. Jain, P. Chand and S. Garg, J. Indian Chem. Soc., 1983, 60, 760.

172. B.J. Sweetman, M. Bellas and L. Field, J. Med. Chem., 1969, 12, 888.

173. M. Wolf and A.A. Mascitti, U.S. Patent, 1969, 3,458,525; Chem. Abstr., 1970, 72, 21715p.

174. B.M. Kirichenko, A.V. Vladzimirskaya and P.M. Steblyuk, Farm. Zh. (Kiev), 1981, 61; Chem. Abstr., 1981, 95, 169060s.

175. G.C. Rovnyak, V.L. Narayanan and R.D. Haugwitz, U.S. Patent, 1977, 4,053, 613; Chem. Abstr., 1978, 88, 22889r.

176. CIBA Ltd., Neth. Appl., 1965, 6,507,422; Chem. Abstr., 1966, 65, 2228f.

177. K.C. Joshi, R. Jain, P. Chand and V. Sharma, Indian J. Chem., 1984, 23, 386.

178. J. Hollowood, Brit. Patent, 1971, 1,239,553; Chem. Abstr., 1971, 75, 98446w.

179. R.J. Bass, Tetrahedron Lett., 1971, 1087.

180. G.I. Zhungietu, N.I. Chmykhova, V.I. Gorgos, M.A. Rekhter and K.S. Khariton, Khim. Getereotsikl. Soedin.,1977, 642; Chem. Abstr., 1977, 87, 83991u.

181. M.A. Rekhter, V.I. Gorgos and G.I. Zhungietu, U.S.S.R. Patent, 1979, 702, 010; Chem. Abstr., 1980, 92, 146597w.

182. G.I. Zhungietu, V.I. Gorgos, M.A. Rekhter and A.I. Korpan, Ser. Biol. Khim. Nauk., 1980, 61; Chem. Abstr., 1980, 93, 239138h.

183. A.C. White and R.M. Black, Ger. Offen., 1972, 2,200,584; Chem. Abstr., 1972, 77, 126681f.

184. A. Romode Vivar and J. Romo, J. Org. Chem., 1959, 24, 1490.

185. E. Wenkert and N.V. Bringi, J. Amer. Chem. Soc., 1958, 80, 5575.

186. H. Otomasu and S. Omiya, Japan Kokai, 1975, 75 137,987; Chem. Abstr., 1976, 85, 46630p.

187. P.J. Islip and A.C. White, J. Chem. Soc., 1964, 1201.

188. K.A. Vbaidullaev, R. Shakirov and S. Yu. Yunusov, Khim. Prir. Soedin., 1976, 553; Chem. Abstr., 1977, 86, 121586e.

189. M. Wolf, U.S. Patent, 1967, 3,314,951; Chem. Abstr., 1967, 67, 90819j.

190. G.I. Zhungietu, L.A. Vlad and F.N. Chukhrii, Khim Getereotsikl. Soedin., 1976, 797; Chem. Abstr., 1976, 85, 123886f.

191. G.I. Zhungietu, L.A. Vlad and F.N. Chukhrii, V sb., Khimiya i Farmacol Indol'n. Soedinenii, 1975, 61; Chem. Abstr., 1976, 84, 121786d.

192. M.S.K. Youssef, Rev. Roum. Chim., 1981, 26, 471.

193. A.B. Tomchin and V.S. Dmitrukha, Zh. Org. Khim., 1975, 11, 184; Chem. Abstr., 1975, 82, 140027g.

194. A.B. Tomchin, Zh. Org. Khim., 1981, 17, 589; Chem. Abstr., 1981, 95, 62139x.

195. A.B. Tomchin, Zh. Org. Khim., 1981, 17, 1561; Chem. Abstr., 1982, 96, 169091c.

196. M. Furukawa, T. Yoshida and S. Hayashi, Chem. & Pharm. Bull., 1974, 22, 2875.

197. D.R. Long and C.G. Richards, Tetrahedron Lett., 1975, 1603.

198. K. Okada, H. Sakuma and S. Inoue, Chem. Lett., 1979, 131.

199. C.G. Richards and M.S.F. Ross, Tetrahedron Lett., 1968, 4391.

200. T. Kato, H. Yamanaka and H. Ichikawa, Chem. & Pharm. Bull., 1969, 17, 481.

201. E.N. Herring and C.G. Richards, J. Pharma. Pharmacol., 1972, 167.

202. U. Simon, O. Sues and L. Horner, Justus Liebigs Ann. Chem., 1966, 17, 697.

203. J. Plostnieks, U.S. Patent, 1967, 3,308,134; Chem. Abstr., 1967, 67, 2994j.

204. G.N. Walker, D. Alkalay and R.T. Smith, J. Org. Chem., 1965, 30, 2973.

205. K.M. Biswas and A.H. Jackson, Tetrahedron, 1969, 25, 227.

206. J.K. Jasper Clark, J. Chem. Soc., 1957, 2202.

207. W.I. Awad and A.H. Lawrence, Tetrahedron, 1970, 26, 5959.

208. C. Riche, A. Chiaroni, H. Doucerain, R. Besselievre and C. Thal, Tetrahedron Lett., 1975, 4567.

209. A. Chiaroni, H. Doucerain and C. Riche, Acta Crystallogr. Sect. B, 1976, B32, 1922.

210. W.G. Brouwer, W.A. Craig, J.A.D. Jeffreys and A. Munro, J. Chem. Soc., Perkin Trans. 1, 1972, 124.

211. G. Kobayashi and Y. Matsuda, Japan Patent, 1970, 70 20,102; Chem. Abstr., 1970, 73, 66461q.

212. T.S.T. Wang, Tetrahedron Lett., 1975, 1637.

213. C. Gref, B. Sabourault and J. Bourdais, Tetrahedron Lett., 1972, 1957.

214. Y. Ban and T. Oishi, Chem. & Pharm. Bull., 1963, 11, 446.

215. Y. Ban and T. Oishi, Japan Patent, 1969, 69 04,986; Chem. Abstr.,1969, 71, 3290w.

216. E. Winterfeld and J.M. Nelke, Chem. Ber., 1970, 103, 1174.

217. E. Winterfeld, Ger. Offen., 1971, 1,956,237; Chem. Abstr., 1971, 75, 63604u.

218. A.T. Poo and M.J. Kornet, J. Heterocycl. Chem., 1971, 8, 479.

219. E.E. Van Tamelen, J. Webber, G.P. Schiemenz and W. Barker, Bioorg. Chem., 1976, 5, 283.

220. T. Oishi, M. Ochiai, M. Nagai and Y. Ban, Tetrahedron Lett., 1968, 497.

221. J.Y. Laronze, J. Laronze, D. Royer, J. Levy and J. Le Men, Bull. Soc. Chim. France, 1977, 1215; Chem. Abstr., 1978, 89, 24190a.

222. N. Aimi, Y. Asada, S. Tanabe, S. Tsuge, Y. Watanabe and S. Sakai, Tennen Yuki Kagobutsu Toronkai Koen Yoshishu, 22nd, 1979, 540; Chem. Abstr., 1980, 93, 114796q.

223. J.Y. Laronze, J. Laronze, D. Royer, J. Levy and J. Le Men, Heterocycles, 1980, 14, 579.

224. V. Paragamian, U.S. Patent, 1974, 3,723,459; Chem. Abstr., 1974, 81, 120595s.

225. V. Paragamian, U.S. Patent, 1974, 3,816,449; Chem. Abstr., 1974, 81, 105483k.

226. V. Paragamian, U.S. Patent, 1974, 3,818,038; Chem. Abstr., 1974, 81, 105327n.

227. V. Paragamian, U.S. Patent, 1974, 3,818,039; Chem. Abstr., 1974, 81, 105326m.

228. F.D. Popp, J. Heterocycl. Chem., 1969, 6, 125.

229. V.M. Dzimko, A.V. Ivashchenko and R.V. Poponova, Zh. Org. Khim., 1974, 10, 1325; Chem. Abstr., 1974, 81, 105443x.

230. A.V. Ivashchenko and I.F. Agafonova, Khim. Getereotsikl. Soedin., 1981, 249; Chem. Abstr., 1981, 95, 7219y.

231. K. Niume, S. Kurosawa, F. Toda, K. Uno and Y. Iwakura, Macromol. Chem. Phys., 1981, 182, 59.

232. A.H. Jackson, D.N. Johnston and P.V.R. Shannon, J. Chem. Soc., Chem. Commun., 1975, 911.

233. G.F. Field, J. Chem. Soc. D, 1969, 886.

234. J.W. Cornforth, J. Chem. Soc., Perkin Trans. 1, 1976, 2004.

235. L. Capuano and K. Benz, Chem. Ber, 1977, 110, 3849.

236. J.W. Clark-Lewis and G.F. Katekar, J. Chem. Soc., 1959, 2825.

237. M.S. Habib and C.W. Rees, Proc. Chem. Soc., 1961, 167.

238. M.S. Habib and C.W. Rees, J. Chem. Soc., 1962, 123.

239. Y. Ahmad, M.S. Habib, M. Iqbal and M.I. Qureshi, J. Chem. Soc., 1964, 4053.

240. Y. Ahmad, M.S. Habib, M. Iqbal, M.I. Qureshi and Ziauddin, Bull. Chem. Soc. (Japan), 1965, 38, 1659.

241. J.L. Diebold and M. Wolf, U.S. Patent, 1973, 3,711,476; Chem. Abstr., 1973, 78, 97672s.

242. F.D. Popp, J. Heterocycl. Chem., 1972, 9, 1399.

243. H. Rapoport and G. Smolinsky, J. Amer. Chem. Soc., 1960, 82, 934.

244. P.M.G. Bavin, Canad. J. Chem., 1965, 43, 2919.

245. A. Kubo, T. Nakai and T. Nozoye, Heterocycles, 1976, 4, 1675.

246. G.C. Morrison, R.O. Waite, F. Serafin and J. Shavel, Jr., J. Org. Chem., 1967, 32, 2551.

247. Warner-Lambert Pharm. Co., French Patent, 1966, 1,434,197; Chem. Abstr., 1966, 65, 16973a.

248. J. Shavel Jr. and O.C. Morrison, U.S. Patent, 1967, 3,314,964; Chem. Abstr., 1968, 68, 49467a.

249. P.P. Righetti, A. Gamba, G. Tacconi and G. Desimoni, Tetrahedron, 1981, 37, 1779.

250. Yu. O. Gabel and V.M. Zubarovskii, J. Gen. Chem., 1937, 7, 305.

251. H. Wexler and A. Caraculacu, An. Stiint Univ. "Al. I. Cuza" Iasi. Sect IC, 1967, 13, 91; Chem. Abstr., 1968, 69, 106525q.

252. H. Wexler and V. Barboiu, Rev. Roum. Chim., 1976, 21, 127.

253. Gj. Stefanovic, M. Pavicic-Woss, Lj. Lorenc and M. Lj. Mihailovic, Tetrahedron, 1959, 6, 97.

254. R.K. Grantham and O. Meth-Cohn, Chem. Commun., 1968, 500.

255. R.K. Grantham, O. Meth-Cohn and M.A. Naqui, J. Chem. Soc. C, 1969, 1438.

256. G.W.H. Cheeseman and S.G. Greenberg, J. Heterocycl. Chem., 1979, 16, 241.

257. W. Steinkopf and H. Wilhelm, Ann., 1941, 546, 211.

258. H. Wexler and A. Caraculacu, An. Stiint Univ. "Al. I. Cuza" Iasi, Sect IC, 1966, 12, 191; Chem. Abstr., 1968, 68, 39450a.

259. L. Geita, I. Dalberga and G. Vanags, Latv. PSR Zinat. Akad. Vestis. Kim. Ser., 1967, 612; Chem. Abstr., 1968, 68, 104931z.

260. J.A. Ballantine, A.W. Johnson and A.S. Katner, J. Chem. Soc., 1964, 3323.

261. P. Bamfield, A.W. Johnson and A.S. Katner, J. Chem. Soc. C., 1966, 1028.

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