

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

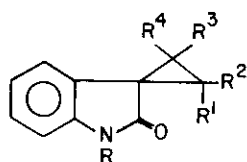
I-1.1) Cyclopropane

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

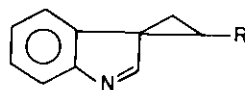
ethane or 1,2-dibromoethane results in the formation of spiro[cyclopropane-1,3'-[3H]indol]-2'(1'H)-ones (1; $R=R^1=R^2=R^3=R^4=H$)¹⁻³. 3-Bromoethylindoles cyclize in a similar manner in the presence of potassium carbonate to give spiro[cyclopropane-1,3'-indolines] (2; $R=H$, COOMe)⁴.

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 diazomethane⁶, or of indolyl tosylate⁷ 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-phenylmethyleindol-2-ones with $PhCOCHSM_2$ ($R=Ac$, Me; $R^1 = COPh$; $R^2=R^4=H$; $R^3 =$ substituted phenyl)⁹.

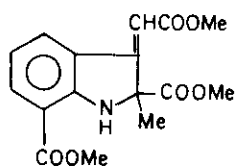
Tryptamine methiodide, on treatment with lithium in ammonia¹⁰ and various indole alkaloids, on vacuum distillation with calcium oxide, zinc dust and palladium, also yield spiro[cyclopropane-1,3'-[3H]indole] derivatives¹¹.



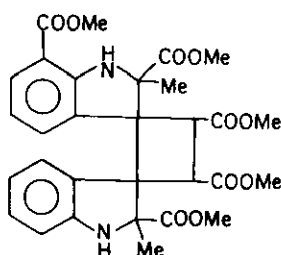
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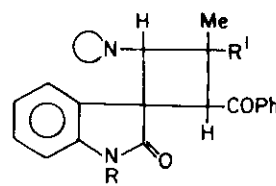
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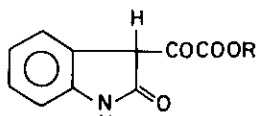
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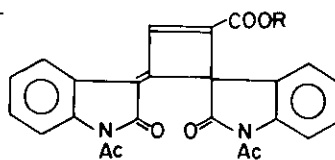
(4)



(5)



(6)



(7)

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 product¹².

Ir spectral studies¹³ and antitubercular activity¹⁴ 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'-[3H]indole] derivatives(4)¹⁷.

The spiro compounds(5; R=Me, Et; R¹=H, Me; $\bigcirc$ = piperidino, pyrrolidino) have also been obtained by 1,2-cycloaddition reaction of N-alkyl substituted 3-oxindolideneacetophenones with enamines¹⁸⁻²⁰.

2-(2-Oxo-3-indoliny)glyoxalates (6; R = Me, Et, CH₂Ph) undergo intramolecular Claisen condensation with acetic anhydride in the presence of pyridine to yield spiro[cyclobutane-1,3'-[3H]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'-[3H]indol]-2'(1'H)-one (8; R = Me; R¹, R²=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; R¹ R² = O; X = CHCOCF₃)²⁵, cyclopentanecarboxylic acid phenylhydrazide with 20% hydrochloric acid(R=R¹=R²=H; X=O)²⁶; photocyclization of N-arylenamines (R=R¹=R²=H; X = H, COOEt)²⁷; 4,4-dialkylhomophthalimide with sodium hypochlorite in alkaline medium²⁸⁻³⁰ and cyclization of PhNRNHCOCHC₅H₉³¹.

Reactions of tetrahydrocarbazole derivatives with PPE or PPA³², arene sulphonylazides³³⁻³⁹, Grignard's reagent⁴⁰, oxidation with sodium metaperiodate⁴¹, thallium diethylmalonate⁴² 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-butoxide⁴⁵ and BF₃.Et₂O⁴⁶ has also been reported. Spiro[cyclopentane-1,2'-ψindoxyl] with Grignard's reagent produce spiro[cyclopentane-1,3'-ψindoxyl] derivatives⁴⁰. During dimerization of (E)-2-oxo-3-indolinylideneacetone, the formation of spiro cyclopentanes is also indicated⁴⁷.

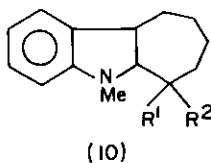
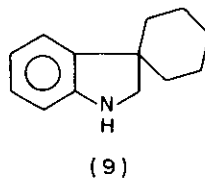
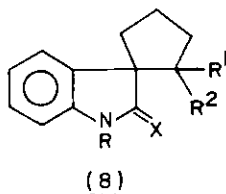
Various reactions like rearrangements⁴⁸⁻⁵⁰, reduction^{43,44}, acetylation^{43,44} and oxidation in presence of mercury lamp⁵¹ of title compounds are reported in the literature. The crystal and molecular structure of 1'-methyl-2-(p-toluenesulfonamido)-2'-(p-toluenesulfonylimino)spiro[cyclopentane-1,3'-[3H]indole] ⁵²

and some other derivatives of this type^{53,54} have been studied by various workers.

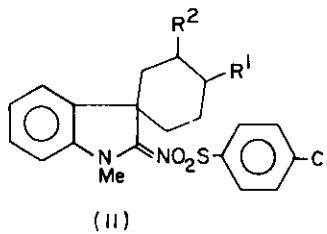
Some of the compounds have been used as basic dyes^{15,16} and biological activities like antiinflammatory³¹, antidepressant⁵⁵ and antihypertensive⁴¹ have been reported to be associated with these structures.

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 cyclization⁵⁶, (ii) Fischer indole cyclization of phenyl hydrazone of acetylhexane with zinc chloride⁵⁷, (iii) Cyclization of 1-methyl-3,3-di(β -carbethoxyethyl)oxindole with potassium in toluene⁵⁸, (iv) Alkylation of 2-oxindoles with 1,5-diiodopentane in presence of butyl lithium⁵⁹, (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 etherate⁶²⁻⁶⁴, (viii) Cyclization of 1-phenyl-2-acylhydrazine with phosphorus oxychloride⁶⁵, (ix) Reaction of tetracyanoethylene with the cyclic adduct obtained by treatment of 3-oxindolidene acetophenone with enamines⁶⁶, (x) Reaction of 4,4-dialkylhomophthalimide with sodium ethoxide in alkaline medium²⁸⁻³⁰, and (xi) Cyclization of $PhNRRNHCOCHC_6H_5$ ³¹.



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



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

Hexahydrocyclohepta-indoles(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 studied⁵⁸.

A number of compounds have been used as analgesics⁵⁶, fungicides⁶⁹⁻⁷¹, anti-depressants⁵⁵ and antiinflammatory agents³¹.

Furthermore, various derivatives are useful as basic dyes^{15,16}, as dye developers for photographic diffusion transfer system⁷² and as photochromic agents⁷³. Some dyes of this series (merocyanine-rhodamines) have been studied with respect to the changes in absorption, fluorescence, dichroism and birifringence in stained giant axons⁷⁴.

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; $\text{R}=\text{H, Me, Ph}$; $\text{R}^1, \text{R}^2=\text{H, H}$; Ph, Ph ; $\text{R}^3=\text{H}$)^{75,76}.
- (ii) Epoxidation of 3-disubstituted methyleneoxindoles with hydrogen peroxide in presence of basic catalyst (12; $\text{R}=\text{H, Me}$; $\text{R}^1=\text{Me, Ph}$; $\text{R}^2=\text{Me, Ph}$; 1-Pr, 4-Py ; $\text{R}^3=\text{H}$)⁷⁷⁻⁸¹.
- (iii) By the reaction of hydrogen peroxide on 3-arylmethyleneindol-2-ones or indolo[2,3-c]pyridazines (12; $\text{R}=\text{H, Me}$; $\text{R}^1=\text{H}$; $\text{R}^2=\text{substituted benzoyl}$; $\text{R}^3=\text{H, OMe}$)^{82,83}.
- (iv) By the reaction of isatin with o-nitrobenzyl chloride (12; $\text{R}=\text{R}^1=\text{R}^3=\text{H}$; $\text{R}^2=\text{o-nitrobenzyl}$)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 isatin⁸⁷.

Some reactions of these indoles and their rearrangements into 2,3-disubstituted indoles have been described by Anthony⁷⁷. The compounds (12; $\text{R}^2=\text{benzoyl}$) 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 aggregation, fungicidal and bactericidal are associated with these compounds^{78,80,81,83,89}.

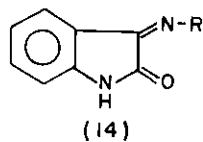
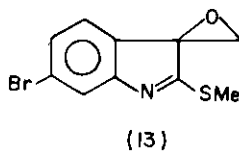
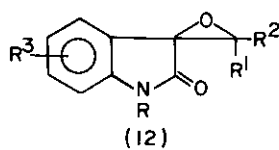
I-2.2) Azete

Hassan and co-workers⁹⁰⁻⁹⁴ 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.

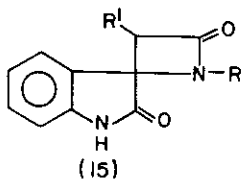
The formation of these β -lactams has also been shown on tlc plates using the same reactants⁹⁵.

I-2.3) Oxete

The thermal 2+2 cycloaddition of $(\text{MeO})_2\text{C}=\text{CH}_2$ 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.

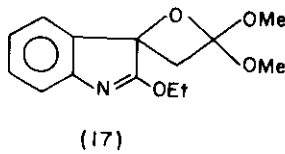
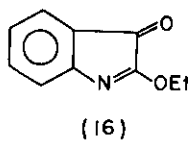


R = Aryl, heterocycle



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R' = Phthalyl, Cl, NH₂



I-2.4) Pyrrole

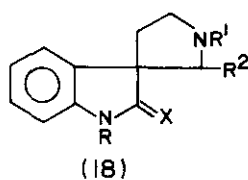
Spiro [3H-indole-3,3'-pyrrolidines] (18) were first prepared from tryptamine/tryptophan derivatives and few examples are cited here :

- (i) Pictet-Spengler type condensation of 3-(2-aminoethyl)-2-oxindole with appropriate aldehyde⁹⁷⁻⁹⁹.

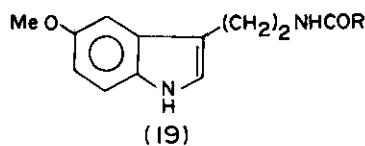
- (ii) The reaction of 3-(2-aminoethyl)indole with aldehyde or NBS^{100,101}.
- (iii) The condensation of 2-hydroxytryptamine hydrochloride with hemiacetals of tetrahydropyran-2-ol in presence of sodium acetate¹⁰².
- (iv) The condensation of 2-hydroxytryptamine hydrochloride with 3-oxobutanol ethyleneketal in basic aqueous ethanol¹⁰³.
- (v) The reaction of methyltryptophan with excess formaldehyde and H ions in the presence of Raney nickel or 5% Pd/C¹⁰⁴.

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

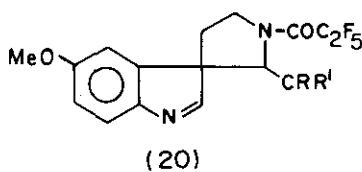
The formation of spiro-pyrrolidines has been reported during the treatment of Mannich bases of indoles with HCl followed by hydrogenolysis¹⁰⁶.



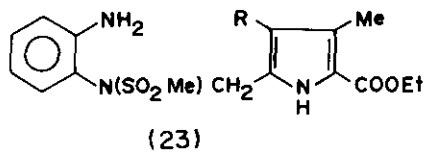
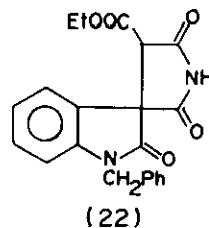
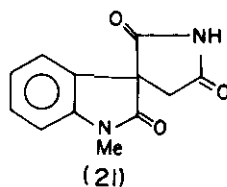
R = H, CH₂OH, CH₂OAc, CH₂OBz;
 R' = H, Bz, Ac, COCMe₃;
 R² = H, Et, Pr, 3,4(OMe)₂C₆H₃,
 3-OH,4-OMe C₆H₃
 X = H₂O



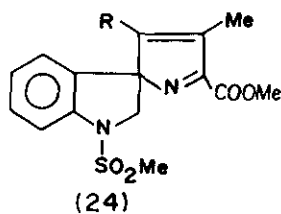
R = Me, Pr, CHMe₂



R = R' = Me
 R = H, R' = Me
 R = H, R' = Et



R = Ac, COOEt



R = Ac, COOEt

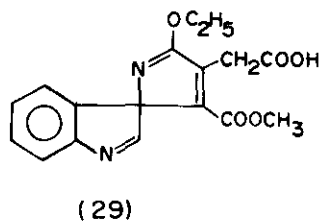
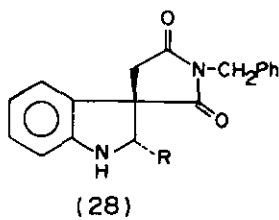
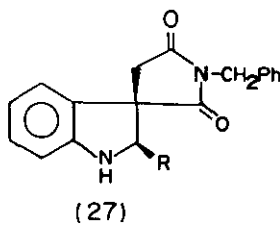
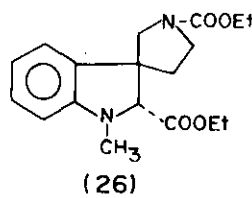
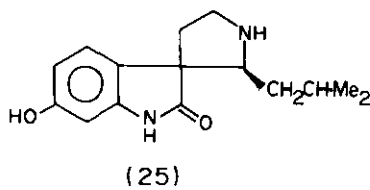
In another approach, 1-substituted isatins have been condensed with cyanoethyl ester followed by the reaction of KCN/HCN to give spiro products 21 and 22^{107,108}.

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 azides¹¹¹⁻¹¹³ and (iii) osmium tetroxide³⁴.

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 intermediate¹¹⁶.

The syntheses of some specific compounds of this series such as (25) from 2,5-Cl(OMe)C₆H₄NH₂ and NC-CH=CH-COOH via a complex of (Ph₃P)₃Ni and aryl halide¹¹⁷, (26) by the photocyclization of N-arylenamines²⁷, (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.



R = Ph, *p*-OMeC₆H₄, Pr, 2-pyrrolyl, Me₃C, etc.

A number of spiro[indole-pyrrolidines] exhibit local anesthetic activity¹⁰⁰,

anticonvulsant activity¹⁰⁸, binding affinity to glycine receptors¹⁰⁹ and other pharmacological activities¹¹¹.

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 compounds¹²⁵. 2-(2-Nitrophenylsulphonyl)indole-3-propionic acid with NBS gives spiro indoline(31)¹²⁶.

Dipeptides of indole with NBS also give similar compounds¹²⁷. Various tryptophan derivatives are frequently oxidized to spiro furans, e.g. (i) oxide of 2-tryptophan with Me₃C-COOH in presence of ferrous sulphate(30; R=NH₂, 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 BrCH₂C(:CH₂)CO₂Et 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 pyranoindoles¹³⁵. Compounds (32) have exhibited anti P-338 lymphocytic leukemia activity¹³³ and some other spiro-furans are active as antiinflammatory¹³², CNS^{132,136} and antihypertensive drugs⁴¹.

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.

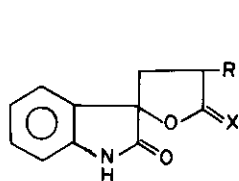
3-(2-Substituted indolyl)thioacrylates (35) undergo cyclization in the presence of HCl-MeOH to give spiro-thiophenes (36)¹³⁷.

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-iminoindolin-3-spiro-thiacyclopentane¹³⁸.

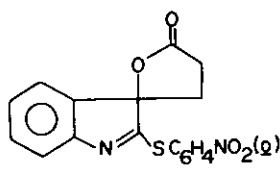
Treatment of 3-(3-methyl-2-oxobutyl)-3-hydroxyoxindole with thionyl chloride gave an unexpected product identified as 3'-chloro-5',5'-dimethyl-spiro[3H-indole-3,2'(3'H)-thiophene]-2,4'(1H,5'H)-dione-1'-oxide (37)¹³⁹.

I-2.7) Pyridine

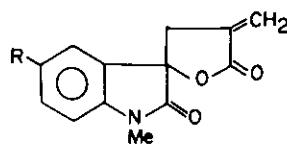
2-Oxindoles, when treated with sodamide and RN(CH₂CH₂Cl)₂, produced the corres-



(30)



(31)

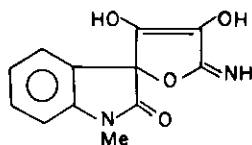


(32)

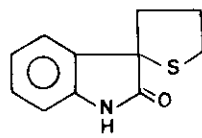
X = H₂, O

R = H, I

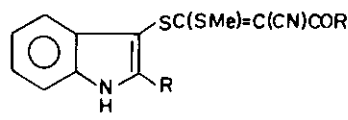
R = H, NHAc, NH₂, phthaloyl



(33)



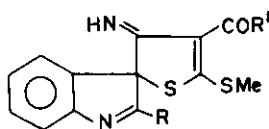
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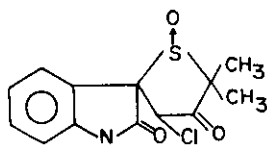
(35)

R = H, Me, Ph

R' = OMe, NH₂, NHHNH₂, NHCH₂-C₆H₅



(36)



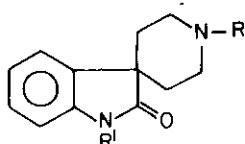
(37)

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 synthesized¹⁴¹⁻¹⁴³. During the Fischer indole cyclization of phenylhydrazine of 4-acetyl-piperidine with zinc chloride, spiro indolines are frequently obtained⁵⁷. The condensation of the derivative of phenacyl cyanide with (ClCH₂CH₂)₂NMe followed by cyclization affords spiro[3H-indole-3,4'-piperidines] (39)¹⁴⁴⁻¹⁴⁸. Kornet and Thio¹⁰⁰ 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 aldehyde¹⁰¹. 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 imines¹⁵⁰ and naphthyridines¹⁵¹ with 4-pyridine-carbonyl chloride. Spiro-piperidines (43; R² = arylsulphonyl) are also obtained by the reaction of arene sulphonyl azides on

tetrahydrocarbolines (42)³⁸.

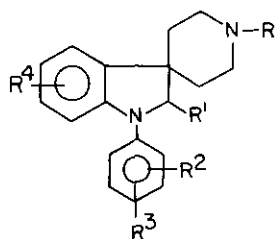
These compounds are of great biological importance and have shown anticonvulsant, antidepressant, tranquilizing, central nerve inhibiting, analgesic, antihypertensive, antirheumatic, local anesthetic, hypotensive, antiinflammatory and ganglion blocking activities^{100,141-148,152}.



(38)

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

R' = H, Ph, alkoxy, C₁₋₄ alkyl, etc.



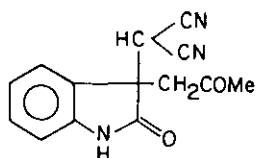
(39)

R = H, alkyl, cyanoalkyl, COOPh, phenylalkyl

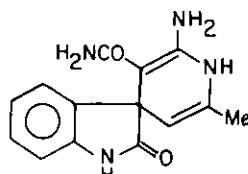
R' = H, alkyl

R², R³ = (Same or different) H, halo, OH, NH₂, CF₃, NO₂, NHAc, alkyl, aryl

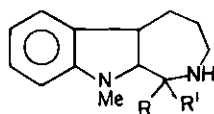
R⁴ = H, halo, OH, alkyl, alkoxy



(40)



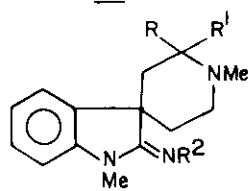
(41)



(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 NBS¹⁵³.

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-diketones¹⁵⁴ and (46) by the reaction of the Michael adduct of acetophenone/acetone with 3-cyanomethyleneoxindoles followed by reaction with NaBH_4 ¹⁴⁹.

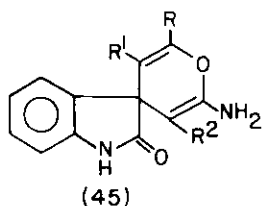
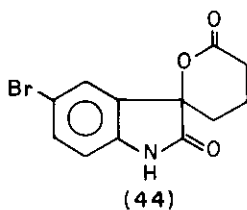
The reaction of compound (47) with isonicotinic acid through various steps has afforded the spiro product (48) which is hypnotic and muscle relaxant¹⁵⁵.

Some of these compounds, useful as antiinflammatory agents, have also been synthesized¹⁴¹.

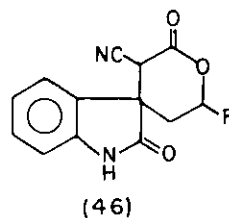
I-3) With Two Heteroatoms

I-3.1) Diazirine

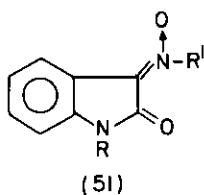
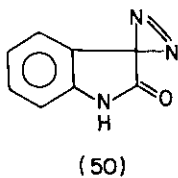
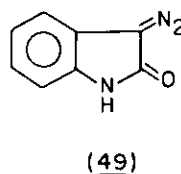
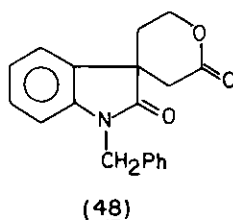
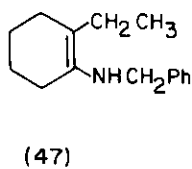
The irradiation of 3-diazoindol-2-one (49) at $\lambda > 290$ nm in methanol, in the early



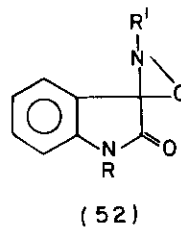
$R = \text{Me}, \text{Ph}, \text{COOMe}$
 $R^1 = \text{H}, \text{Ac}, \text{Bz}, \text{COOEt}$
 $R^2 = \text{CN}, \text{COOEt}$



$R = \text{Me}, \text{Ph}$



$R = \text{H}, \text{Me}; R^1 = \text{Me}, \text{Ph}$



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 discussed¹⁵⁷.

1-3.2) Oxazirine

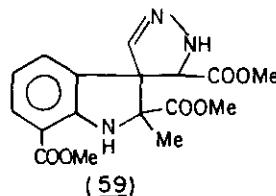
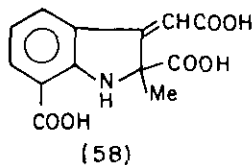
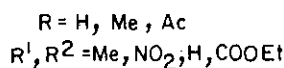
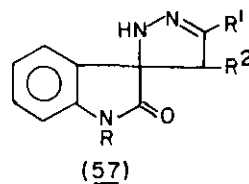
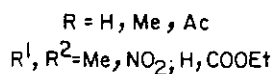
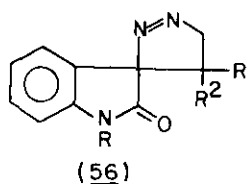
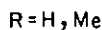
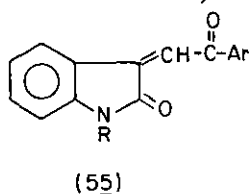
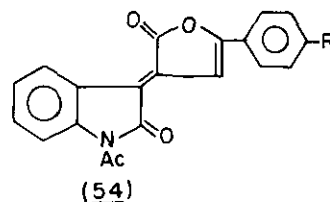
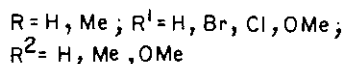
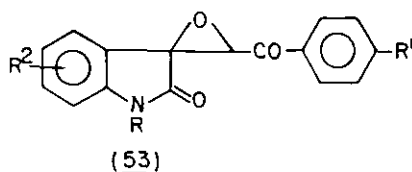
During the photolysis of nitrones of isatin (51) spiro[3H-indole-3,3'-oxaziridin]-2(1H)-ones (52) are reported to have been formed¹⁵⁸.

1-3.3) 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 acids¹⁵⁹ and 3-arylmethyleneindol-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 unsuccessful¹⁶¹.



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 analgesic⁸⁸, antiphlogistic⁸⁸ and blood platelet aggregators⁸⁹.

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 galactosemia¹⁶²⁻¹⁶⁴.

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 derivatives¹⁶⁵.

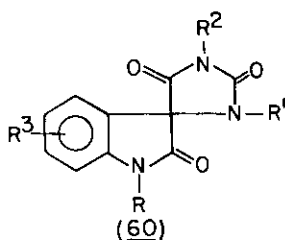
The condensation of 3-arylmethyleneindol-2-ones with benzaldoximes has yielded spiro[3H-indole-3,5'-[2]isoxazolin]-2-ones (63; R=H,Me; R¹=substituted phenyl; R²=substituted benzoyl)¹⁶⁶ and 3-methylene ester of indol-2-one produces (63; R=H,Me; R¹=Ph; R²=CO₂Et) with phenyl cyanate⁸.

Synthesis and properties of some polymers containing spiro[indoline-isoxazoline] system have also been reported¹⁶⁸.

These compounds are useful as CNS drugs¹⁶⁶, antiinflammatory agents¹⁶⁶ and blood platelet aggregators⁸⁹.

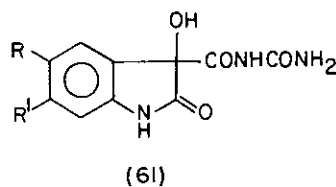
I-3.6) Thiazole

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 reaction¹⁷⁰. 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)-trione¹⁷⁴. Rovnyak et al.¹⁷⁵ have prepared the spiro compound (66) from oxindole and chloroethyl isothiocyanate in glyme containing sodium hydride.

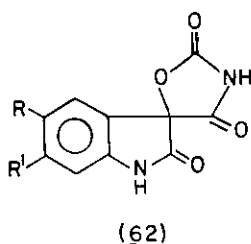


R = H, alkyl, CH₂Ph, aryl; R¹ = H, Me

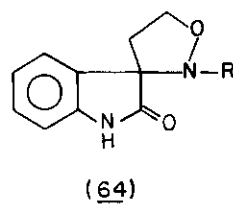
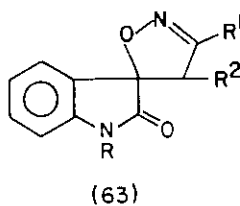
R² = H; R³ = H, OH, NO₂, halo, alkyl



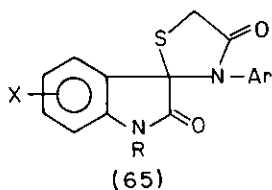
R, R¹ = H or Me



R, R¹ = H or Me

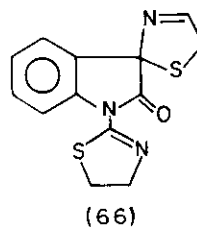


R = Ph, 4-ClC₆H₄, 4-Me₂N-C₆H₄



X = H, F, CF₃; Ar = Subs-phenyl

R = H, alkyl, acyl, morpholinomethyl



These products are useful as pharmaceuticals, antiinflammatory agents^{173,175}, fungistatic¹⁷⁴, bacteriostatic¹⁷⁴ and antiradiators¹⁷².

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

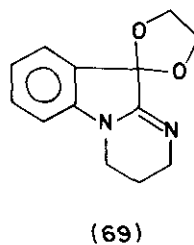
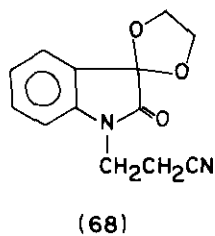
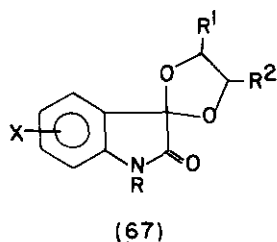
Isatin, on condensation with mercaptodiphenylacetic acid, affords 4',4'-diphenyl-spiro[3H-indole-3,2'-[1,3]oxathiolane]-2,5'(1H)-dione (70) in presence of p-toluenesulphonic acid and desulphurization of the compound has also been carried out¹⁸⁴.

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 reactions¹⁸⁵.

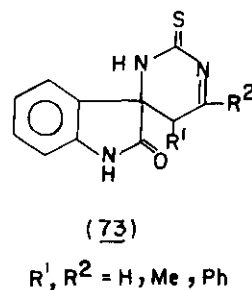
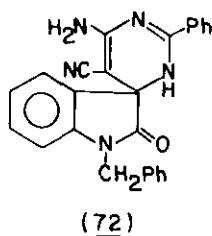
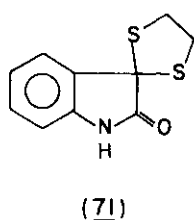
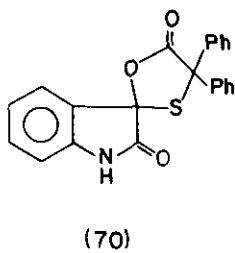
I-3.10) Pyrimidine

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-dicyanomethyleneindol-2-one and $C_6H_5C(:NH)NH_2 \cdot HCl$ in alkaline methanol¹⁸⁶. 3-Aroylmethyleneindol-2-ones also affords spiro products (73) on reacting with thiourea⁹⁴.



R = H, Me, CD₃, COCH₃, CH₂COAr

R', R² = H, Me; X = H, F, CF₃



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-acetyloxindole oxime in ethanolic hydrochloric acid over platinum oxide, followed by treatment with ketones¹⁸⁷ and compound (74; R=H, R¹=Me) can also be prepared by cyclocondensation of 3-hydroxy-3-(N-methylaminoethyl)-2-

oxindole with acetaldehyde¹⁸⁸.

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 atom¹⁷⁷.

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 activities¹⁸⁹.

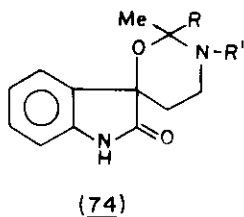
I-3.14) 1,4-Diazepine

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}.

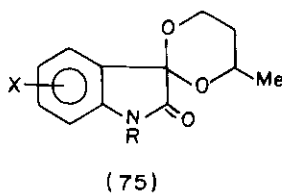
I-4) With Three Heteroatoms

I-4.1) Triazole

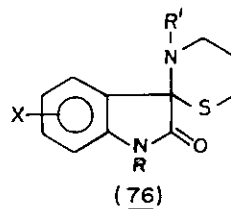
Spiro [3H-indole-3,4'-[4H-1,2,3]triazol]-2(1H)-ones (79) are prepared by treating isatin-3-anils with diazomethane in ether at 0°C for 21 days¹⁹².



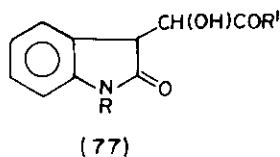
R = H, Me, Ph
R' = H, Me



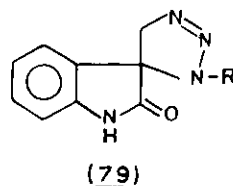
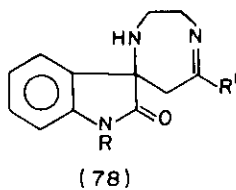
R = H, COCH₃
X = H, F



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.



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



R = aryl, thienyl,
5-bromothieryl, 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 cyanate⁸.

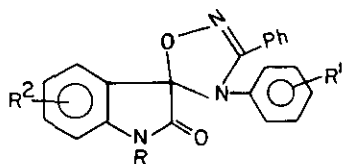
I-4.3) Thiadiazole

The condensation of isatin with phenylthiocarbonylhydrazide 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'H)-[1,3,4]thiadiazol]-2(1H)-ones (82)^{194,195}.

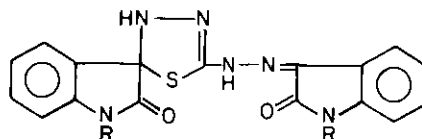
I-4.4) Triazine

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), respectively¹⁹⁶.



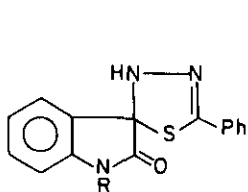
(80)

R = H, Me; R' = H, F, R² = H, F, Me, NO₂



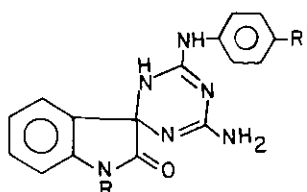
(81)

R = H, Me, pentyl



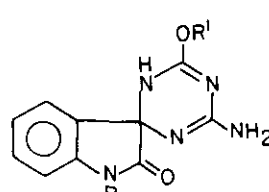
(82)

R = H, Me, Et



(83)

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



(84)

R = H, Me
R' = alkyl

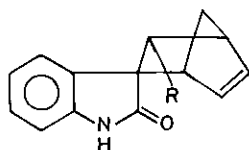
II. TWO RING SYSTEMS

II-1) With No Heteroatom

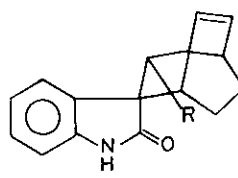
II-1.1) Bicycloheptane/octane

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=NO₂) and 3-nitro-spiro[bicyclo[2.2.2]oct-5-ene-2,3'-[3H]indol]-2'(1'H)-one (86;

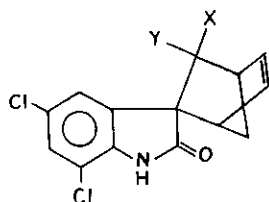
$R=NO_2$)¹⁹⁷. Other 3-substituted methylene-2-oxindoles also produce a mixture of two stereoisomers of (85) and (86) ($R=COOMe$, $COMe$, $COPh$) with cyclopentadiene or cyclohexadiene¹⁹⁸⁻²⁰⁰. E-5,7-Dichlorooxindolylidene-chloroacetonitrile affords two isomeric spiro compounds 87 and 88 with cyclopentadiene²⁰¹. Photolysis of 1-methyl-3-diazooxindole in cyclohexene has been reported to produce the spiro-bicycloheptenes⁵. A spiro product (89) is obtained on irradiation of 2,3,3-triphenylindoline in cyclooctene²⁰².



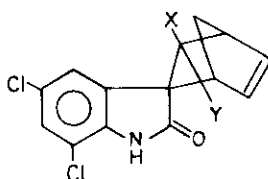
(85)



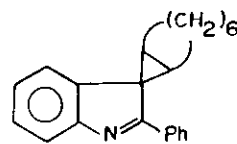
(86)



(87)



(88)



(89)

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

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 pentoxide²⁰⁵.

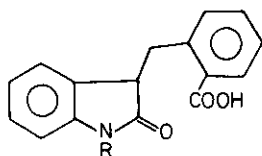
II-1.3) Naphthalene

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

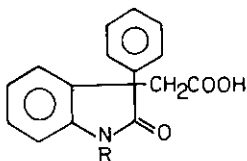
Spiro[3H-indole-3,7'-p-tridecamethylene benzene]-2(1H)-one (95) has been formed by the reaction of p-(7-hydroxy-8-oxotetradecamethylene)benzene with phenyl-

hydrazine²⁰⁶.

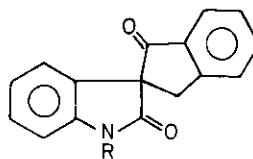


(90)

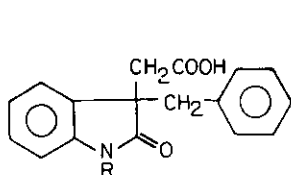
R = H, Me



(91)

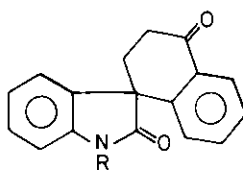


(92)

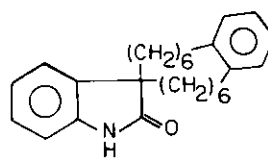


(93)

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.

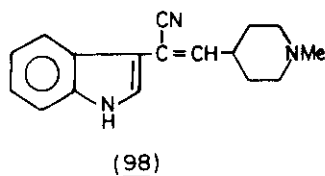
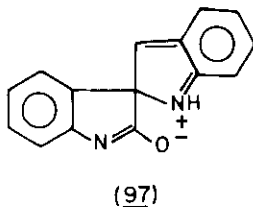
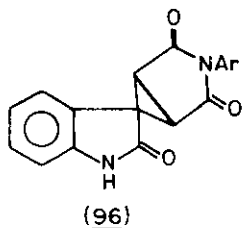
II-2.3) Pyrindene

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 out²⁰⁹.

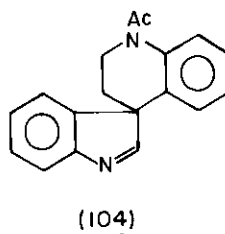
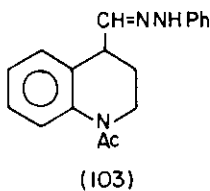
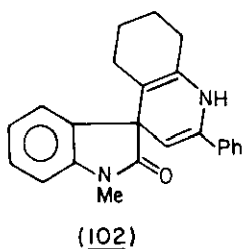
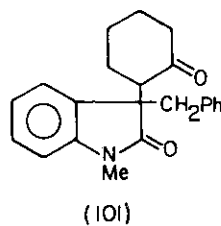
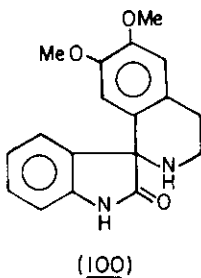
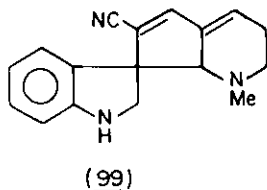
II-2.4) Quinoline and Isoquinoline

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 drug²¹¹.

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



Ar = Ph, *o*- & *p*- tolyl



1-Methyl-3-carboethoxy-3-(*o*-nitrobenzyl)-indol-2-one on reduction with Pd/C also affords spiro quinolines²¹³.

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}.

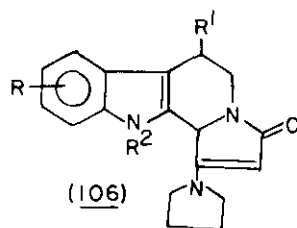
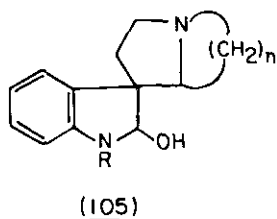
II-2.6) Indolizine

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

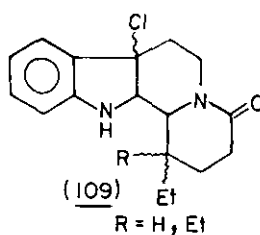
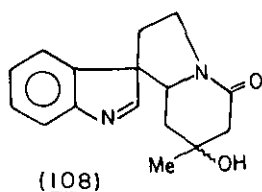
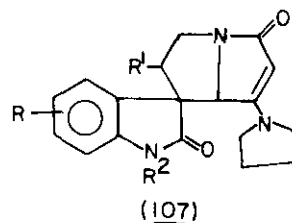
- (i) By the reaction of 5-chlorovaleraldehyde with 2-hydroxytryptamine hydrochloride (105; $R=H$, $n=4$)^{214,215}.
- (ii) Hydrogenation of 3-(2-piperidylmethylene)-2-oxindole followed by treatment with formaldehyde (105; $R=H$, $n=4$)²¹⁸.
- (iii) The treatment of p-nitrophenyl-3-indole acetate with $H_2N(CH_2)_4CH(OEt)_2$ 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.

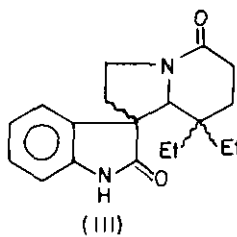
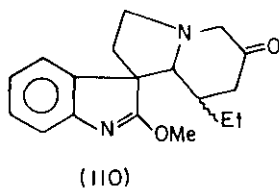
The spiro compounds 110 and 111 are obtained from condensed indole derivatives (109) on treatment with acetic acid, potassium hydroxide and methanol²²¹.



$R, R', R^2 = H, H, Et; H, Me, Me;$
 $7-Me, H, Me; 5-OMe, H, Me$



$R = H, Et$



The oxidation of 3-oxotabursonine with potassium permanganate afforded a similar compound²²².

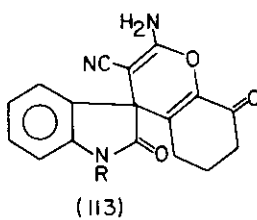
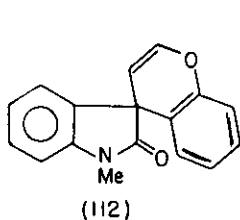
Mass spectral fragmentations of the compounds have also been described²²³.

II-2.7) Benzopyran

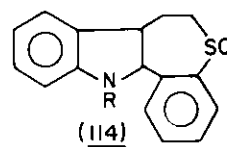
1-Methyl-3-(2-oxocyclohexyl)-3-phenacyloxyindole, when refluxed in methanolic HCl, affords spiro [4H-benzopyran-4,3'-[3H] indol]-2'(1'H)-one (112) which displayed antiinflammatory action¹⁴¹. 3-Dicyanomethyleneindol-2-one, with 1,3-cyclohexanedione, gives the spiro product (113)¹⁵⁴.

II-2.8) Thiochroman

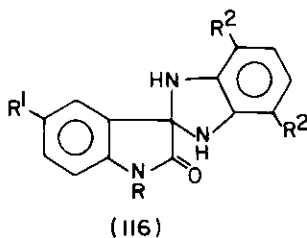
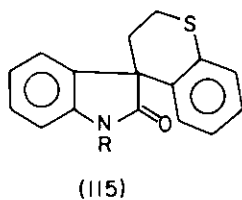
Benzothiepineindoles (114) on treatment with HCl, give spiro [3H-indole-3,4'-thiochroman]-2(1H)-ones (115). The former compounds are obtained from 5-oxo-2,3,4,5-tetrahydrobenzo[b] thiepin and phenylhydrazine hydrochloride. The



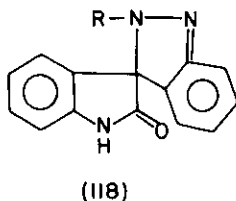
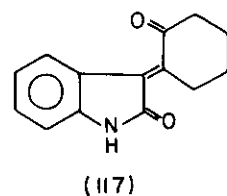
R = H, Me



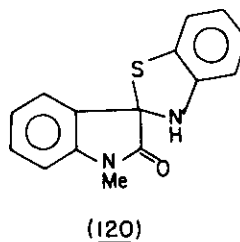
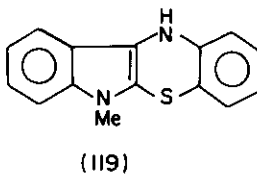
R = CH₂CH₂CN, CH₂CH₂COOH,
CH₂CH₂COOEt



R = H, Ac, Me; R' = H, NO₂
R² = 1, 4-dibutoxy, 1, 4-heptyloxy



R = H, Ph



compounds have been used to inhibit the gastric acid secretion in rats²²⁴⁻²²⁷.

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-dione²²⁸⁻²³⁰.

Polymers of these compounds are obtained when polycondensation of bisatyls is carried out with aromatic tetramines in polar organic solvents²³¹.

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 ethanol²³².

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

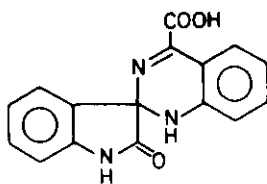
Quinoxaline carboxanilides (124) isomerize to spiro[3H-indole-3,2'(3'H)-quinoxaline]-2,3'(1H)-diones (125; R=same or different Cl, H, MeO, Me; R¹=H, Ac, Me; R²=Me, H) in the presence of concentrated sulphuric acid at 0°C or hot ethanolic hydrochloric acid. If R² is an electron withdrawing group, the reaction does not take place with sulphuric acid²³⁶⁻²⁴⁰.

II-3.6) Benzoxazine

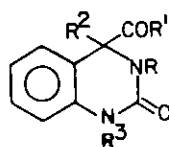
Diebold and Wolf refluxed isatin with o-NH₂C₆H₄CH(OH)Ph in xylene in presence of zinc chloride to obtain 6-chloro-1,4-dihydro-4-phenyl-spiro[2H-3,1-benzoxazine-2,3'-[3H]indol]-2'(1'H)-one (126) which has been found to possess bactericidal and CNS depressant activity²⁴¹.

II-3.7) Benzodiazepine

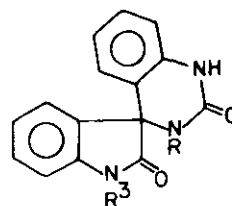
Indolyl carbinols afford spiro[2H-1,5-benzodiazepine-2,3'-[3H]indole]derivatives (127) on treatment with 1,2-phenylenediamines^{190,191}.



(121)

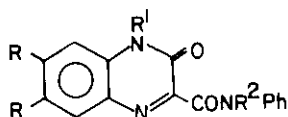


(122)

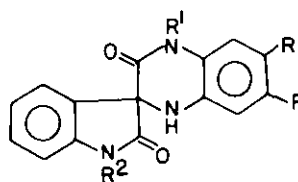


(123)

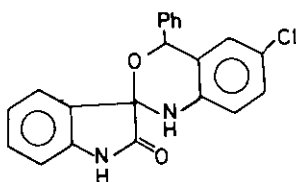
$R = \text{Me, Ph}; R^1 = \text{NHPh, NHNBz};$
 $R^2 = \text{OH}; R^3 = \text{H, Me}$



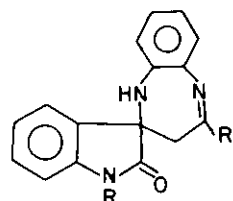
(124)



(125)



(126)



(127)

$R = \text{H, Me}$
 $R^1 = \text{Ph, p-tolyl}$

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-pyrazolone¹⁵⁴.

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

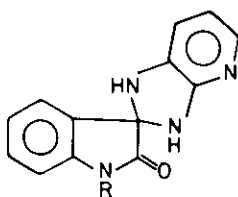
Isatin and 4,5-diaminopyrimidine produce 1,3-dihydro-spiro[2H-imidazo[4,5-d]pyrimidine-2,3'-[3H]indol]-2'(1'H)-ones (131)²⁴².

III. THREE RING SYSTEMS

III-1) With No Heteroatom

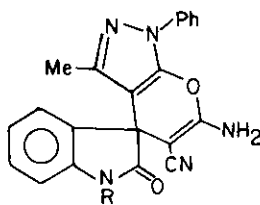
III-1.1) Fluorene

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 Bavin²⁴⁴ through the cyclization of 9-benzoylfluorene with phenylhydrazine.



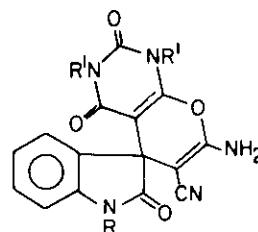
(128)

R = H, COCH₃



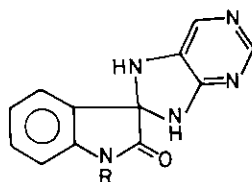
(129)

R = H, Me



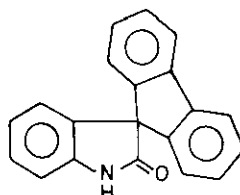
(130)

R, R' = H, Me

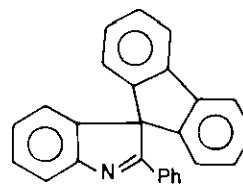


(131)

R = H, COCH₃



(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 products²⁴⁵.

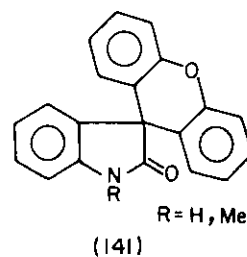
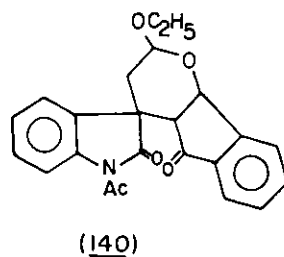
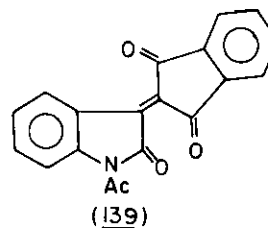
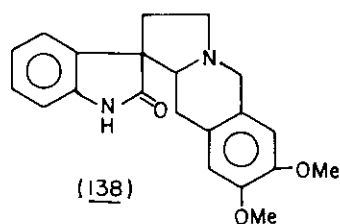
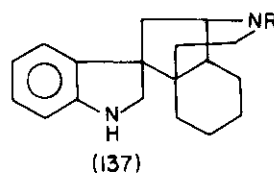
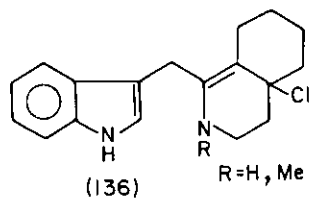
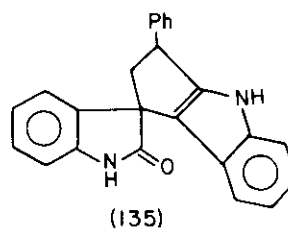
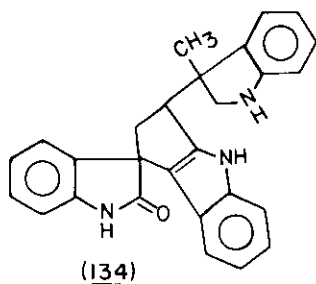
III-2.2) Iminoethanoindan

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-oxindolylethylamine hydrochloride with 3,4-dimethoxyphenyl-acetaldehyde gave spiro[3H-indole-3,1'-pyrrolo[1,2-c]isoquinoline] derivative (138)⁹⁷.



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 $\text{EtOCH}=\text{CH}_2$ 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)-trione²⁵³.

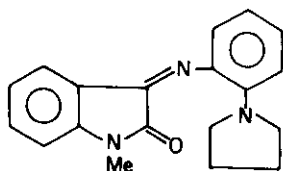
III-3) With Two Heteroatoms

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

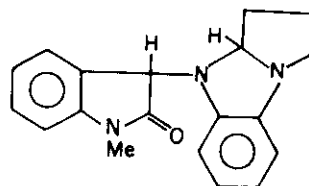
Tetrahydro-spiro[3H-indole-3,4'(5'H)-pyrrolo[1,2-a]quinoxalin]-2(1H)-one (144) is obtained by the treatment of either anil (142) or tetrahydropyrrole[1,2-a]benzimidazole (143) with acid or ethanol^{254,255}.

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

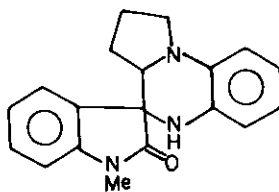
The cyclization of N-(o-aminomethylphenyl)pyrrole hydrochloride with isatin in DMF affords 5,6-dihydro-spiro[3H-indol-3,4'-[4H]pyrrolo[1,2-a][1,4]benzodiazepin]-2(1H)-one (146)²⁵⁶.



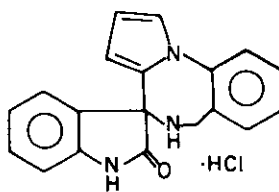
(142)



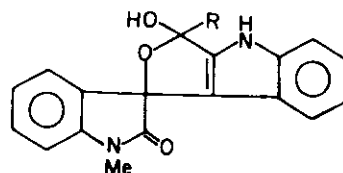
(143)



(144)



(145)



(146)

R = Me, Ph

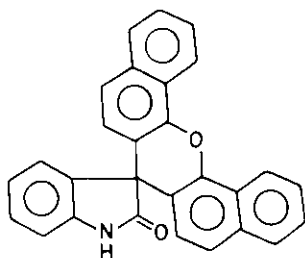
III-3.3) Furo[3,4-b]indole

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 acid²⁵⁷.

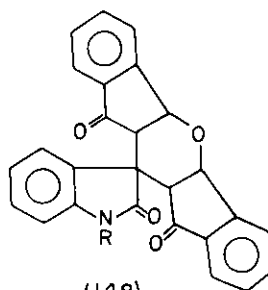
MISCELLANEOUS

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.

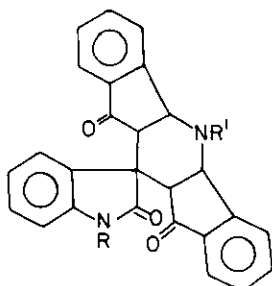
The reaction product of isatin with acetic anhydride and pyridine has been shown to be (150)²⁶⁰.



(147)



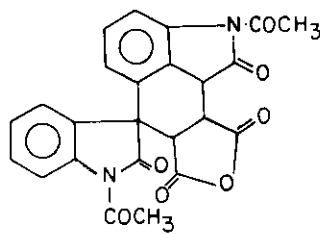
(148)

R = H, COCH₃

(149)

R = H, COCH₃

R' = H, Ph



(150)

Oxindolylidene-acetone has been shown to react with a variety of acetylenic dienophiles to yield various derivatives of naphthostyrils²⁶¹.

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