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Synthesis of spiro[piperidine-4,C'_n-hetero(carbo)cycles]

R A Kuroyan
The A L Mndzhoyan Institute of Pure Organic Chemistry of the Academy of Sciences of the Armenian SSR, Erevan, Armenia

ABSTRACT. **A systemic survey is presented on methods of preparing *N*-containing spiroheterocycles in which a piperidine ring is spiro-condensed at the four position with various carbocycles and heterocycles. The biological properties of these compounds is also discussed.**

The bibliography contains 250 references.

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I. Introduction

In recent years much attention has been focussed on methods of preparing spiroheterocycles, in particular spiro-N-heterocycles, and studying their biological activity. This was intensified after the isolation of the biogenic amine, histrionicotoxin, from the skin of the tree frog, *Dendrobates histrionicus*.[1] This amine is a derivative of 1-azaspiro[5.5]undecan-8-ol, having highly unsaturated groups at the 2- and 7-positions, the structure and absolute configuration of which has been established by X-ray analysis. Subsequently, more than ten other 1-azaspiro[5.5]undecanes having a variety of unsaturated functions at the same ring positions were isolated from the genus *Dendrobates*.[2–5] In view of the biological significance of histrionicotoxin (which blocks the transmission of nervous impulses following activation by acetylcholine[1,6,7]), and because it is difficult to isolate in large amounts from the tree frog, much research has been devoted to the chemical synthesis of histrionicotoxin and variously hydrogenated derivatives.

Racemic octahydrohistrionicotoxin has been prepared by several routes, but, at the present time, no total synthesis of histrionicotoxin itself has been reported, primarily because of the lability of the unsaturated residues. A review published in 1982[8] covers this aspect, but since this time new data has been published, largely in connection with stereoselective and non-stereoselective routes to variously hydrogenated histrionicotoxin derivatives.[9,10] A further impetus to research in this field came with the discovery that the biological activity of histrionicotoxin is not entirely associated with the unsaturated functions in the side chain. For example, perhydrohistrionicotoxin—2-amyl-7-butyl-1-azaspiro[5.5]undecan-8-ol—has a biological activity very similar to that of histrionicotoxin. The development of non-stereoselective and stereoselective routes to 1-azaspiro[5.5]undecanes has already born fruit.[11–25]

At the beginning of the 1980's, Yunusov, et al. isolated the alkaloids, nitramine, isonitramine and sibirine, from *Nitraria schoberi, Nitraria sibirica* and *Nitraria sibirica Pall*, respectively.[26,27] These compounds were shown to have the 2-azaspiro[5.5]undecane skeleton, the first two having an asymmetric centre at C_7. Although the biological properties of these alkaloids are unknown, much work has been published on their non-stereoselective and stereoselective synthesis.[28–34]

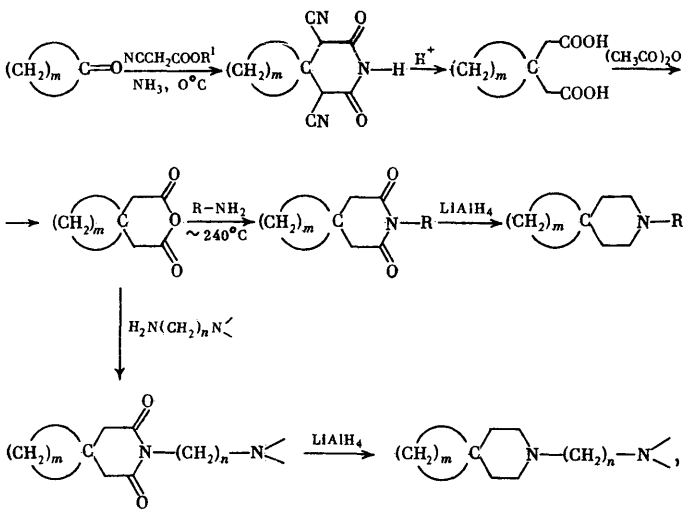
Spirocycles without a nitrogen atom have also been isolated from plants and living organisms. Thus, the components of the pheromone complex from the olive fly, *Dacus olfae*, have the 1,7-dioxaspiro[5.5]undecane skeleton.[35] Although few spiro compounds have been isolated from nature, there is sufficient evidence that spiroheterocycles perform key biological functions. It is for this reason that much research has been devoted both to the synthesis of analogues of spiro-fused alkaloids and biogenic amines, and to methods of preparing new spiroheterocyclic bases. Such compounds possess a wide spectrum of biological activity, and certain derivatives have been used medicinally, notably as pyschotropic drugs.[36–38]

The volume of literature on the synthesis of spiroheterocycles and the study of their chemistry and biological activity is so large that it would be impossible to digest in one review. The present review covers the methods of preparing, and the biological activity, of nitrogen-containing spiroheterocycles in which a piperidine ring is spiro-fused at the 4-position with a variety of carbo- and heterocycles. However, there has been no attempt to present an all-embracing review of the literature. Rather, the objective has been to highlight the problems which chemists have experienced in the synthesis of such compounds as potential drugs.

II. Spiro-*N*-heterocycles in which a piperidine ring is spiro-condensed at the four position with carbo- and heterocycles

It was in the 1960's that research into the synthesis and biological activity of spirocycles, such as azaspiranes, commenced. 1,1-Bis-(carboxymethyl)-carbocycles and -heterocycles were the key intermediates used for the preparation of azaspiranes in which a piperidine ring is spiro-fused at the 4-position by various carbo- and heterocycles. The well-established route to such intermediates involves interaction of a ketone with ethyl cyanoacetate under mild conditions in ammonia-saturated ethanol to give the corresponding Guareschi's imide, subsequent hydrolysis of which affords the desired *gem*-disubstituted diacetic acid.[39] The latter are then

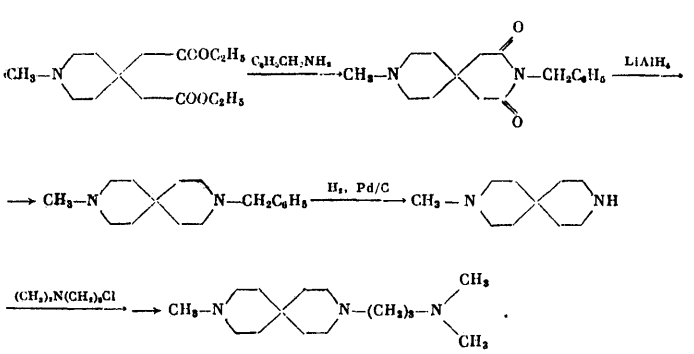
converted to the corresponding cyclic anhydride spiro-fused with a variety of carbo- and heterocycles, and subsequent treatment with a whole range of amines or diamines yields the corresponding imide in reasonably high yield. These undergo hydride reduction, as shown below.[40–57]



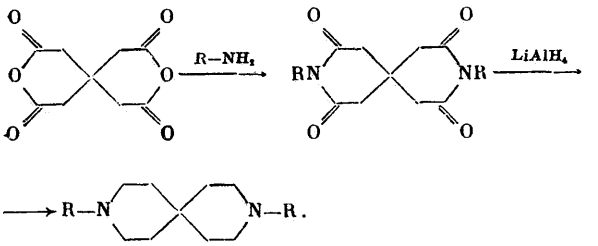
R = H, alky, isoalkyl, aryl; n = 2, 3; m = 2–7.

Depending on the nature of the substituent on the piperidine nitrogen and the nature of the ring fused at C_4, the resulting 3-azaspiranes and their salts display a variety of biological activities. The compounds act on the central nervous system,[40–43,46–49,55,57] possess analgesic,[41] antihypertensive,[41–43,45–47] antihistamine,[48] antimicrobial and antibacterial activity,[40,41] and suppress the growth of tumour cells.[52–54] In certain instances, the intermediate 3-azaspirane-2,4-diones were submitted to biological tests and shown to have both antimicrobial[58,59] and, notably, psychotropic activity.[60–63]

The above-described 3-azaspirane synthesis is also applicable to 1-methyl-4-piperidone as the cyclic ketone, so that it is possible to prepare diazaspiranes having two piperidine rings spiro-fused at the 4-position. The intermediate 1-methylpiperidine-4,4-diacetic acid was converted to the diethyl ester (rather than the cyclic anhydride), which reacted with benzylamine to give the corresponding imine; hydride reduction of the latter then gave the desired 3-benzyl-9-methyl-3,9-diazaspiro[5.5]undecane, as shown below. Cleavage of the *N*-benzyl group was effected by hydrogenation over palladium-on-carbon, and the resulting secondary amino function was further alkylated to give, for example, the γ-(dimethylamine)propyl derivative as a useful intermediate for the preparation of pharmacologically active agents.[64,65]

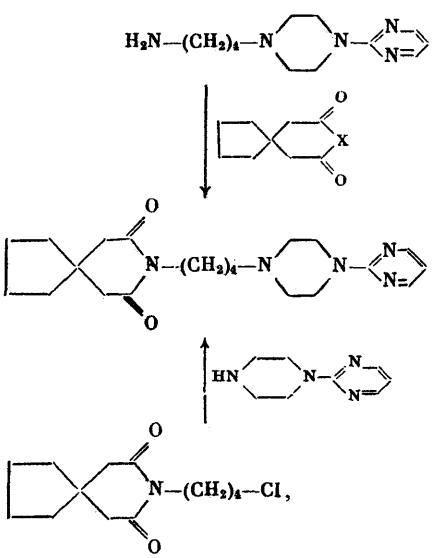


In an alternative synthesis of 3,9-diazaspiranes, methanetetraacetic acid was converted to its spirocyclic bisanhydride, which afforded the desired product on treatment with primary amine followed by hydride reduction.[64]



The main advantage of the previous route over this alternative procedure is that the resulting diazaspiranes may have different substituents on the two nitrogen atoms.

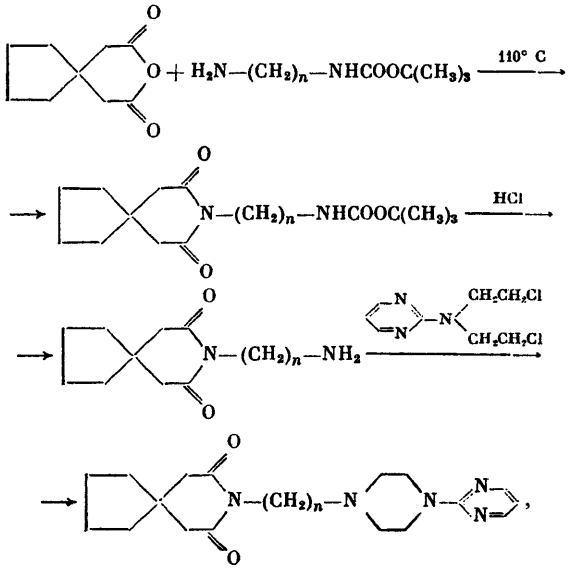
One of the 3-azaspiranes obtained by the first method is 8-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-8-azaspiro[4.5]decane-7,9-dione, which displays neuroleptic properties and is used medicinally under the name buspirone.[66] In one synthesis of this drug, 3,3-tetramethyleneglutaric anhydride is converted to the corresponding imide with 1-(4-aminobutyl)-4-(2-pyrimidinyl)piperazine in pyridine; alternatively, it can be prepared by interaction of *N*-(4-chlorobutyl)-3,3-tetramethyleneglutarimide with *N*-(2-pyrimidinyl)piperazine in butanol.[67,68]



X=O, NH.

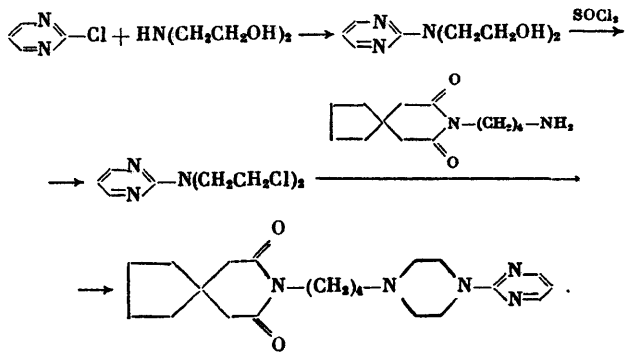
In recent years, a variety of methods has been used for the synthesis of buspirone and its analogues. Thus, treatment of 3,3-tetramethyleneglutaric anhydride with *tert*-butyl *N*-(ω-aminoalkyl)carbamates affords the corresponding imides, which undergo

selective hydrolysis to the corresponding *N*-ω(aminoalkyl)-3,3-tetramethyleneglutarimides. Interaction of the latter with 2-[*bis*(2-chloroethyl)amino]pyrimidine gives buspirone and its analogues in high yield, according to the following scheme.[69]



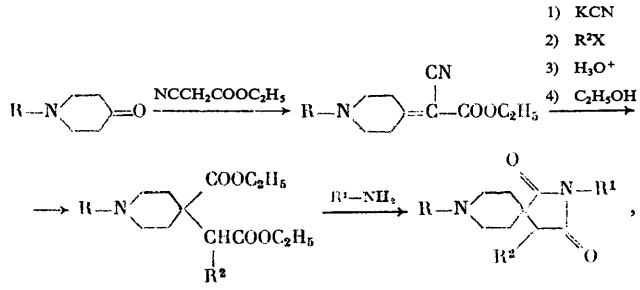
$n = 2-5$.

Buspirone was also obtained by the route shown below. Thus, 2-chloropyrimidine interacts with diethanolamine to give *N*-(2-pyrimidinyl)diethanolamine, which is converted to the corresponding bis(2-chloroethyl)amine with thionyl chloride. Subsequent condensation with *N*-(ω-aminobutyl)-3,3-tetramethyleneglutarimide affords the desired compound in high yield.[70]



Other routes to buspirone,[71-73] its precursors,[74] and novel analogues[75-78] have been reported. For diagnostic purposes, a buspirone derivative having a dideuteriated piperazine ring has also been prepared.[79]

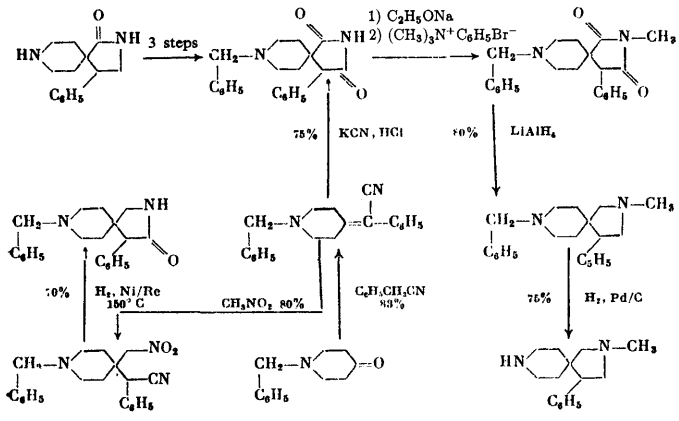
The Knoevenagel reaction has been applied in a useful synthesis of azaspiranes in which a piperidine ring is spiro-fused at the 4-position with a succinimide ring. The latter may have a variety of substituents in the 2- and 4-positions. Thus, 4-piperidones condense with ethyl cyanoacetate to give the Knoevenagel product, which undergoes Michael addition with HCN to give the corresponding dicyanoester; hydrolysis of the latter, followed by decarboxylation and esterification affords the corresponding *gem*-disubstituted diethyl succinate, which reacts with primary amines to give the desired 2-substituted 2,8-diazaspiro[4.5]decanes.[80-87] The same authors have also prepared spirosuccinimides with substituents in both the 2- and 4-position. This was achieved by hydrolysing the dicyanoesters, and then α-alkylating (or α-arylating) with various alkyl (or aryl) halides prior to succinimide ring closure.[81]



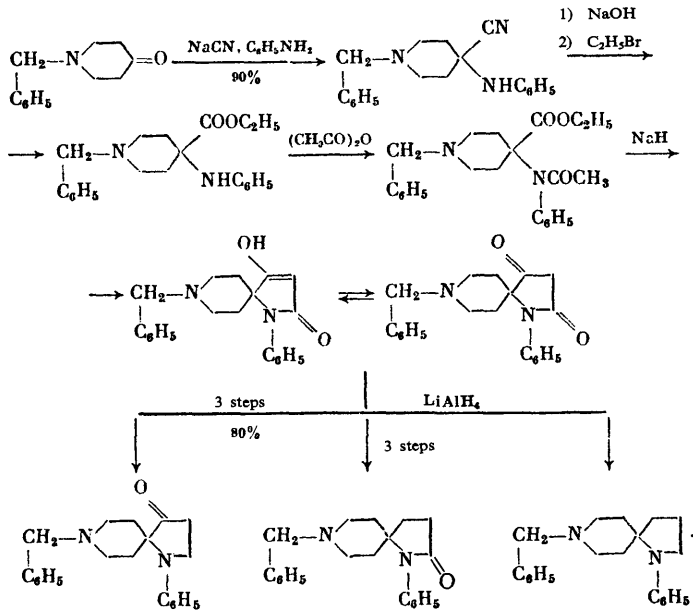
R = H, alkyl, isoalkyl, phenyl, benzyl, phenylethyl, allyl, benzoylethyl; R^1 = H, alkyl, isoalkyl, allyl, phenyl, benzyl, phenylethyl; R^2 = H, alkyl, isoalkyl, aryl, allyl.

Having prepared *N*-benzylpiperidine derivatives by this route, the benzyl group may then be readily cleaved by standard methods to give the corresponding *N*-unsubstituted derivatives; the latter may then be *N*-alkylated to give compounds with potential pharmacological activity. Thus, alkylation with 3-chloropropyl *p*-fluorobenzoate affords an azaspirosuccinimide with neuroleptic activity.[82,83]

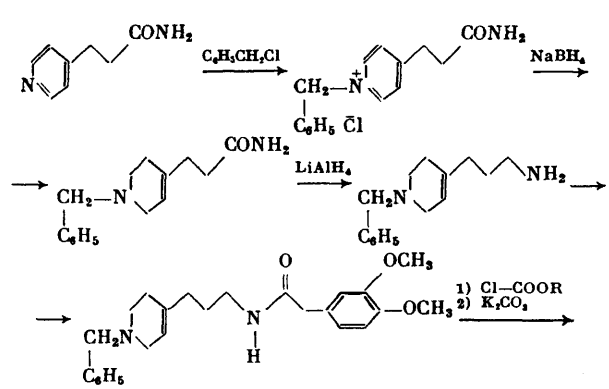
In a modification of the above 2,8-diazaspiro[4.5]decane synthesis, it is also possible to prepare azaspiranes with a phenyl group. Thus, Knoevenagel condensation of *N*-benzyl-4-piperidone with phenylacetonitrile, followed by addition of HCN leads to the corresponding dinitrile by Michael addition; without isolation, this is cylised with HCl to give 4-phenyl-8-benzyl-2,8-diazaspiro[4.5]decane-2,4-dione, which is partially or completely reduced to give 4-phenyl-8-benzyl-2,8-diazaspiro[4.5]decane or the corresponding 1-oxo- and 3-oxo-derivatives.[88] The latter may also be prepared by addition of nitromethane to α-[*N*-benzylpiperidin-4-ylidene]benzyl cyanide, followed by hydrogenation over Raney nickel under pressure.[88] These conversions are shown below.

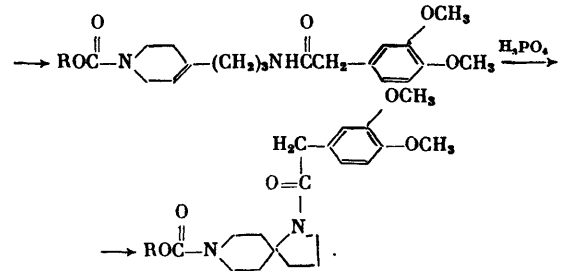


1,8-Diazaspiro[4.5]decanes have also been synthesised from *N*-benzyl-4-piperidone. Thus, treatment of the latter under Strecker conditions affords 1-benzyl-4-cyano-4-anilinopiperidine, from which the corresponding α-anilinocarboxylic acid ethyl ester is obtained and then *N*-acetylated with acetic anhydride. Subsequent intramolecular Dieckmann cyclisation provides *N*-benzyl-1-phenyl-1,8-diazaspiro[4.5]decane-2,4-dione (in 45% yield), which is completely or partially reduced to 8-benzyl-1-phenyl-1,8-diazaspiro-[4.5]decane or the 2-oxo- and 4-oxo-derivatives, as shown below.[89]

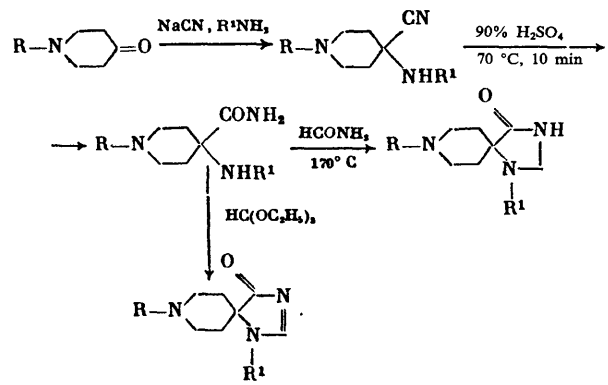


Alternatively, the 1,8-diazaspiro[4.5]decane ring can be prepared from 4-(2-carbamylethyl)pyridine. Thus, treatment of the latter with benzyl chloride affords the corresponding *N*-benzylpyridinium salt, which undergoes sequential reduction, first with $NaBH_4$ to give 1-benzyl-1,2,3,6-tetrahydro-β-(4-pyridyl)propionamide, reduction of which with $LiAlH_4$ affords the corresponding 3-substituted propylamine. Condensation of the latter with 3,4-dimethoxyphenylacetic acid gives the corresponding amide (in 70% yield), which, in the key step, is converted to the *N*-carbalkoxy derivative by treatment with chloroformic acid ester. Cyclisation with 80% phosphoric acid then provides the desired 1,8-diazaspiro-[4.5]decane.[90]



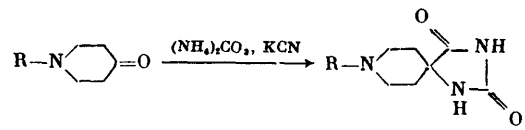


In an extension of these routes, biologically active 1,3,8-triazaspiro[4.5]decanes have also been prepared from 4-piperidones. The synthesis involves Strecker conversion to the corresponding α-aminonitriles, followed by hydrolysis to the corresponding amides and cyclisation of the latter with formamide or ethyl orthoformate.[91,92]

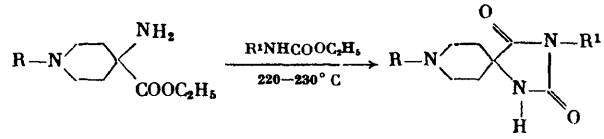


A large number of 1-phenyl-1,3,8-triazaspiro[4.5]decan-4-ones have been prepared by this route by varying the substituent on the piperidine nitrogen atom. These have been shown to possess neuroleptic,[93–95] tranquilizing,[96–98] analgesic,[97–101] sedative,[100,105] hypotensive, and antiinflammatory[97] activities, and, furthermore, are apomorphine antagonists and CNS depressants.[102–104] One of these compounds—8-[3-(4-fluorobenzoyl)propyl]-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one—is a neuroleptic drug used medicinally under the name 'spiperone'.[106] Labelled spiperone derivatives having an isotopic carbon, fluorine, iodine or bromine atom have also been prepared for diagnostic purposes.[107–114]

The 1,3,8-triazaspirane skeleton also incorporates spiro[piperidine-4,5′-hydantoins], obtained in high yield by interaction of 4-piperidones with a mixture of KCN and ammonium carbonate.[115–120]



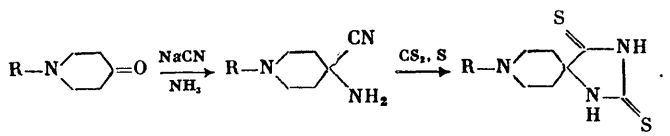
Such spirohydantoins are also obtainable by condensing 4-amino-4-ethoxycarbonylpiperidines with *N*-substituted carbamates.[121,122]



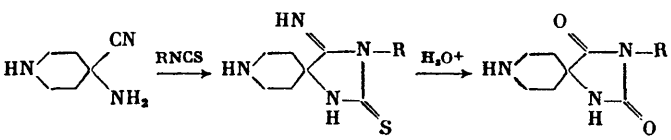
R = phenyl, benzyl; R^1 = alkyl, cyclohexyl, phenyl.

Spirohydantoins possess analgesic, antispasmolytic and antiinflammatory activities.

Antiinflammatory 1,3,8-triazaspiro[4.5]decane-2,4-dithiones are obtained from 4-piperidones via Strecker synthesis, followed by treatment of the resulting α-aminonitriles with carbon disulphide.[123]

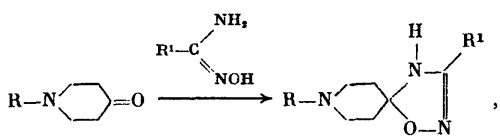


These same α-aminonitriles interact with isothiocyanates to provide a new route to 4-imino-1,3,8-triazaspiro[4.5]decane-2-thiones,[124] hydrolysis of which leads to the corresponding hydantoins.[125]



R = alkyl, cyclohexyl, phenyl, α-naphthyl.

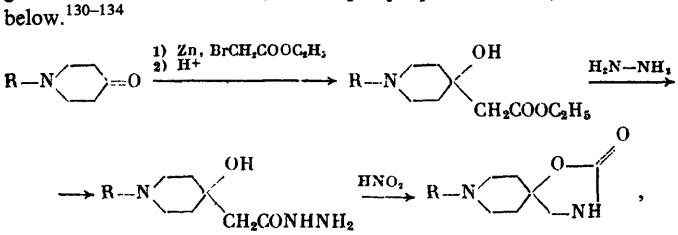
Piperidines spiro-fused with the 1,2,4-oxadiazoline ring have been prepared by interaction of 4-piperidones with amidoximes in the presence of various acids.[126–129]



R = H, alkyl, acyl, aryl; R^1 = alkyl, phenyl, benzyl, *p*-tolyl.

Such 1-oxa-2,4,8-triazaspiro[4.5]dec-2-enes possess sedative, analgesic, and antiinflammatory activity, and reduce blood levels of sugar and cholesterol.

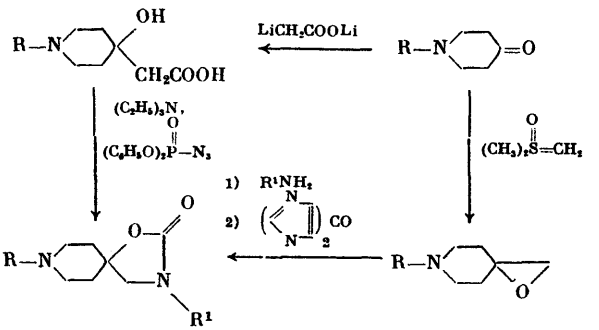
Piperidines spiro-fused at the 4-position with the 2-oxazolidone ring have been obtained via Reformatskii reaction with 4-piperidones. The resulting β-hydroxycarboxylic acid esters are converted to the corresponding hydrazides which undergo Curtius rearrangement to give the desired 1-oxa-3,8-diazaspiro[4.5]decan-2-ones, as shown below.[130–134]



R = alkyl, aryl.

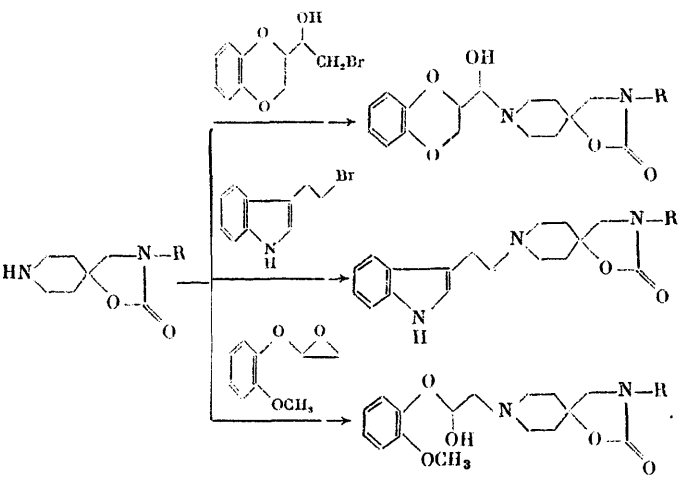
These compounds possess antiinflammatory, antiasthmatic, analgesic, and tranquillizing activity.

A wide range of 1-oxa-3,8-diazaspiro[4.5]decan-2-ones has been prepared by other researchers, both by the route shown above and by two other methods.[135] One of these is based on the conversion of 4-piperidones to the corresponding spirooxirane which is cylised to the desired 1-oxa-3,8-diazaspiro[4.5]decan-2-ones in two steps. Alternatively, in a one-step route, the same products are obtained by interaction of 4-carboxymethyl-4-hydroxypiperidines with diphenyl phosphorazidate.[135]

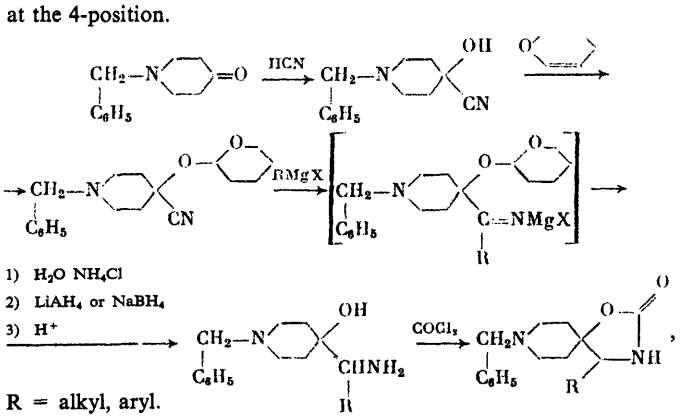


R^1 = H, alkyl.

Treatment of 1-oxa-3,8-diazaspiro[4.5]decan-2-ones with a variety of halides or epoxides affords *N*-substituted derivatives with antihypertensive properties.[135]



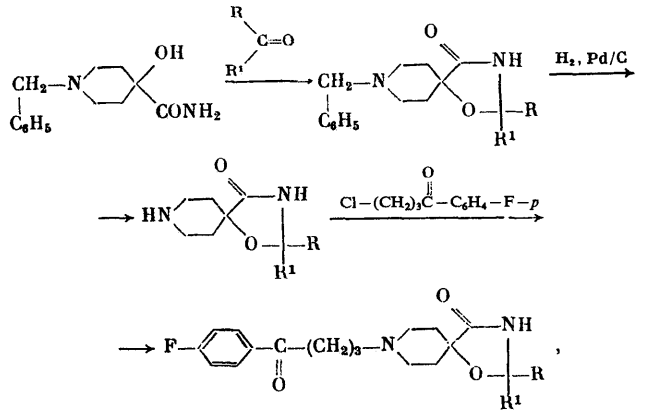
In an alternative 1-oxa-3,8-diazaspiro[4.5]decan-2-one synthesis, 4-piperidone cyanohydrins are protected as their tetrahydropyran-2-yl ethers, which afford the corresponding 2-aminoalcohol derivatives by reaction with Grignard reagents followed by reduction and deprotection. Cyclisation with phosgene then secures the desired spirocyclics.[136] This method has been applied to the preparation of 1-oxa-3,8-diazaspiro[4.5]decan-2-ones with a variety of substituents at the 4-position.



R = alkyl, aryl.

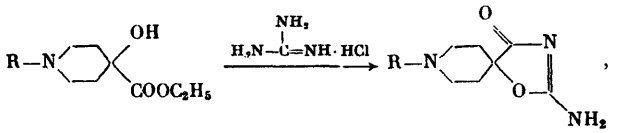
Debenzylation of these compounds, followed by *N*-alkylation (notably with 2-chloromethyl-1,4-benzodioxane) leads to *N*-substituted derivatives which possess pharmacological activity and are suitable for the treatment of diseases of the cardiovascular system.[137]

1-Oxa-3,8-diazaspiro[4.5]decan-4-ones have been prepared by interaction of 1-benzyl-4-hydroxypiperidine-4-carboxamide with carbonyl compounds in acidic media. Subsequent debenzylation and *N*-alkylation with 3-(4-fluorobenzoyl)propyl chloride affords the desired spirocyclics which possess neuroleptic, cataleptic, adrenolytic, and sedative properties.[138]



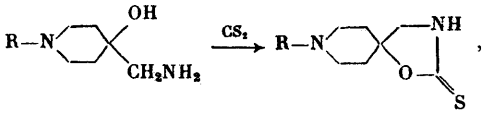
R = H, methyl; R^1 = methyl, phenyl, benzyl.

Condensation of 4-carbethoxy-4-hydroxypiperidines with guanidine hydrochloride affords 2-amino-1-oxa-3,8-diazaspiro-[4.5]dec-2-en-4-ones which display CNS depressant activity.[139]



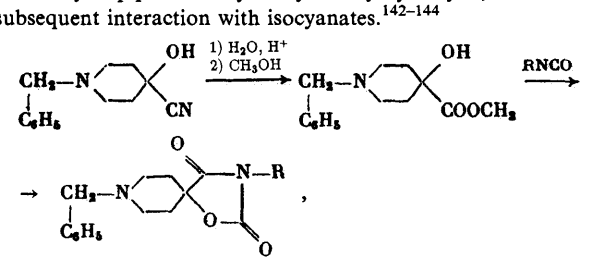
R = H, alkyl, aralkyl.

1-Oxa-3,8-diazaspiro[4.5]decane-2-thiones have been prepared by interaction of 4-aminomethyl-4-hydroxypiperidines with carbon disulphide.[140,141] Compounds of this type possess neuroleptic, broncodilator, analgesic, antibacterial, and hypotensive properties.



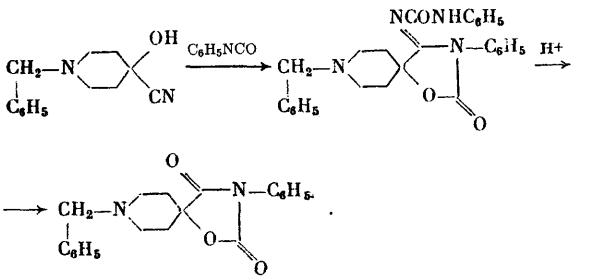
R = benzyl, 4-fluorobenzoylpropyl.

1-Oxa-3,8-diazaspiro[4.5]decane-2,4-diones have been synthesised from *N*-benzyl-4-piperidone cyanohydrin by hydrolysis, esterification, and subsequent interaction with isocyanates.[142–144]



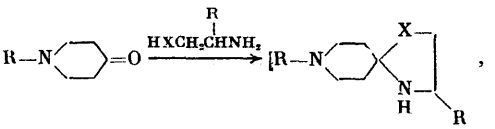
R = alkyl, benzyl, aryl.

The same authors have prepared 8-benzyl-3-phenyl-4-phenylcarbamylimino-1-oxa-3,8-diazaspiro[4.5]decan-2-one from the same cyanohydrin and phenyl isocyanate; hydrolysis of the product in acidic media leads to 8-benzyl-3-phenyl-1-oxa-3,8-diazaspiro-[4.5]decane-2,4-dione.[145]



Derivatives of this ring system possess CNS depressant activity.

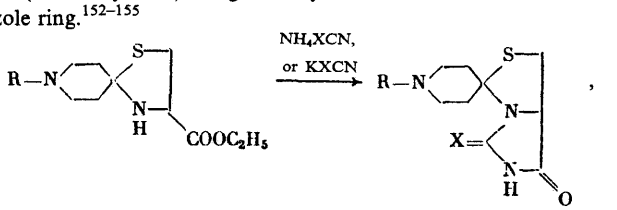
A general method of preparing 1-oxa-4,8-diazaspiro[4.5]decanes and 1-thia-4,8-diazaspiro[4.5]decanes has also been devised. This is based on the interaction of 4-piperidones with 2-aminoalcohols and 2-aminomercaptans, respectively, under acidic catalysis.[146–149]



X = O, S; R = H, alkyl, phenyl, acetyl, ethoxycarbonyl; R^1 = H, carboxyl, ethoxycarbonyl.

For the preparation of 1-thia-analogues, a mixture of the corresponding aziridine and hydrogen sulphide may be used in place of 2-aminomercaptans.[149]

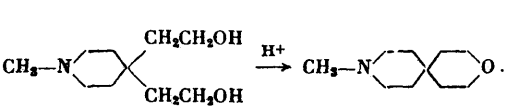
Similar results have been obtained by using *N*-substituted 2-aminoalcohols.[150,151] Compounds in this class possess analgesic,[146,147] psychotropic, CNS stimulatory,[146–148] and antibacterial activity.[149] 1-Thia-4,8-diazaspiro[4.5]decanes with an ethoxycarbonyl group at the 3-position react further with potassium or ammonium cyanate (or thiocyanate) to give tricyclic derivatives with a fused imidazole ring.[152–155]



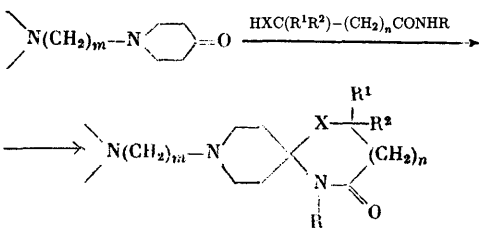
X = O, S; R = H, alkyl, acyl, aryl, ethoxycarbonyl.

Of the numerous derivatives with this ring system, some have shown neuroleptic properties,[155] while others display anti-hallucinogenic, sedative,[152] psychotropic,[153] and antithromotoxic properties.[154]

9-Methyl-3-oxa-9-azaspiro[5.5]undecane has been prepared from 1-methyl-4,4-*bis*(2-hydroxyethyl)piperidine by heating in an acidic medium.[156] The substrate is obtainable by reduction of the 4,4-*bis*-(carboxymethyl) derivative with $LiAlH_4$.



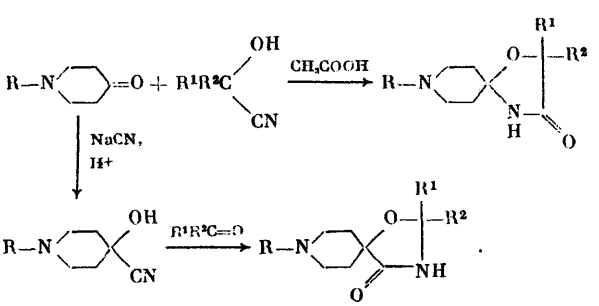
Much research has been devoted to the synthesis of derivatives of 1-oxa- or 1-thia-4,8-diazaspiro[4.5]decan-3-one and 1-oxa- or 1-thia-5,9-diazaspiro[5.5]undecan-4-one.[157–187] All routes to these compounds are based on *N*-substituted 4-piperidones, which cyclise to the desired spirocyclics on reaction with various hydroxy- or mercapto-carboxylic acids under acidic catalysis.



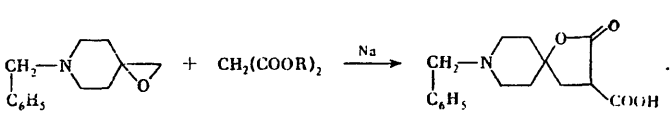
R = H, alkyl, aryl, benzyl, 2-furfuryl, 2-pyridyl; R^1 and R^2 = H, alkyl, phenyl; n = 0, 1; m = 2, 3; X = O, S, SO, SO_2.

Similar results are obtained if the hydroxy- or mercapto-carboxamides are replaced by a mixture of the corresponding hydroxy- or mercapto-carboxylic acid and a primary amine or ammonium carbonate.[188–193] Interest in these spiroheterocyclic systems has increased since certain of the compounds possess CNS stimulating activity,[161] reserpine antagonist,[158,163] tranquillizing,[167,173] analgesic,[167,179] psychotropic,[168,169,180,192] depressant,[191] neuroleptic,[174] and antiinflammatory[160,172,184] activities; certain compounds also reduce cholesterol levels,[159,184] the toxicity of carbon tetrachloride in the liver,[157,166] and sugar levels in the blood;[158] certain also suppress the activity of acetylcholine, and are used in the treatment of intestinal spasms and ulcers;[186] sedative and anticonvulsant activities have also been reported.[187] It should be noted that a number of these compounds are used medicinally as drugs.

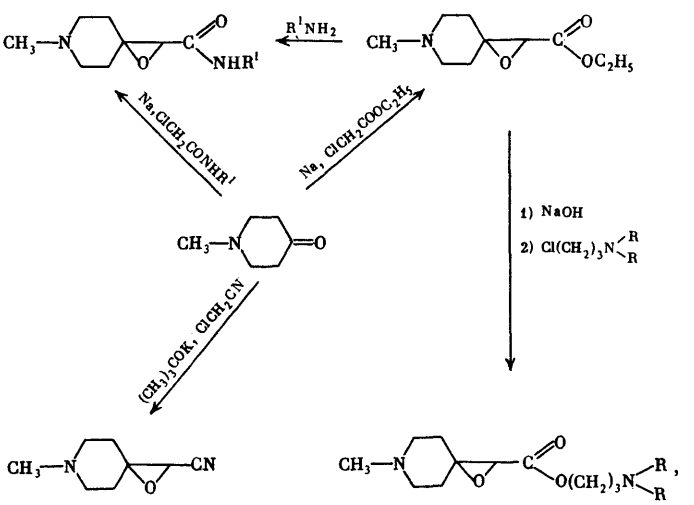
1-Oxa-4,8-diazaspiro[4.5]decan-3-ones have also been obtained by condensation of 4-piperidones with cyanohydrins.[194] Treatment of 4-cyano-4-hydroxypiperidines with ketones, however, leads to 1-oxa-3,8-diazaspiro[4.5]decan-4-ones.[194]



1-Oxa-6-azaspiro[2.5]octanes interact with malonic acid esters to give 3-carboxyazaspirocyclic lactones.[195]



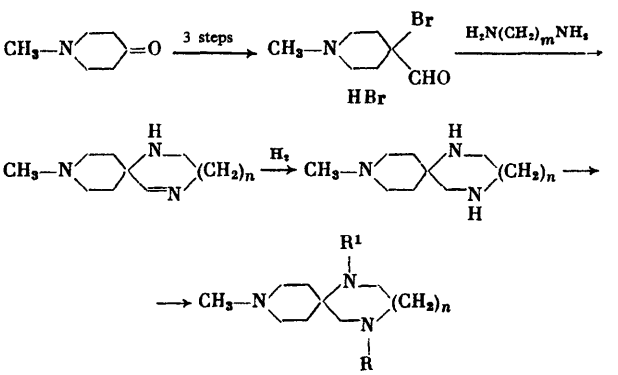
Derivatives of 1-oxa-6-azaspiro[2.5]octane having a carbalkoxy, amino-substituted carbalkoxy, carbamyl, or cyano groups at the 2-position have been prepared from 4-piperidones by the Darzens condensation.[196–199] For the cyano derivatives, potassium *tert*-butoxide was used as base, while metallic sodium was preferred for the preparation of the other derivatives.



R = methyl, ethyl, piperidyl, morphoyl; R^1 = H, methyl, ethyl, phenyl.

The mass spectrometric fragmentation of aminoalkyl 1-oxa-6-azaspiro[2.5]octane-2-carboxylates has been studied.[200]

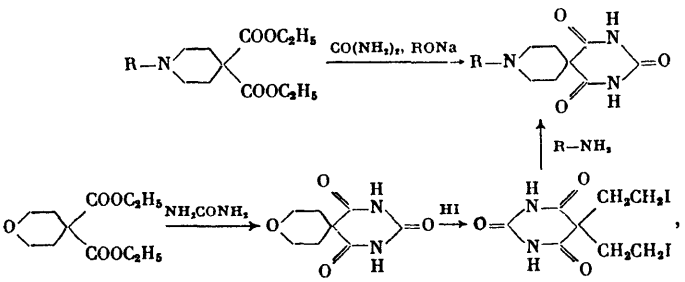
Spirocyclics with a piperidine ring spiro-fused at the 4-position with the piperazine or perhydrodiazepine ring (or partially dehydrogenated derivatives) have also been prepared.[201,202] It has been shown that the nitrogen atom situated alpha to the spirocarbon atom in both 9-methyl-1,4,9-triazaspiro[5.5]undecane and 3-methyl-3,7,11-triazaspiro[5.6]dodecane is relatively unreactive, so that it is possible to prepare both mono- and di-*N*-substituted derivatives.



R=CH_2CH_2CN, CH_2CN, CH_2CONH_2, $CH_2CH_2CONH_2$, $CH_2COOC_2H_5$, $CH_2CH_2COOC_2H_5$, $CH_2CH_2NH_2$, $(CH_2)_3-NH_2$, $CH_2CONHNH_2$; R'=H, $CH_2COOC_2H_5$, $CH_2CONHNH_2$; m=2, 3; n=1, 2.

2,4,9-Triazaspiro[5.5]undecane-1,3,5-triones have been prepared by two different routes. One is based on the cyclocondensation of 4,4-bis(carbethoxy)piperidines with urea in the presence of sodium

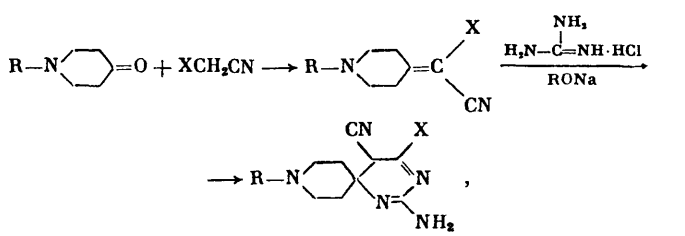
ethoxide, while the other involves cyclisation of 5,5-bis-(2-iodoethyl)barbituric acids with primary amines.[203] These barbituric acids are obtainable from 9-oxa-2,4-diazaspiro[5.5]-undecane-1,3,5-trione, as shown below.[204]



R = alkyl, allyl, aryl, benzyl, cyclohexyl.

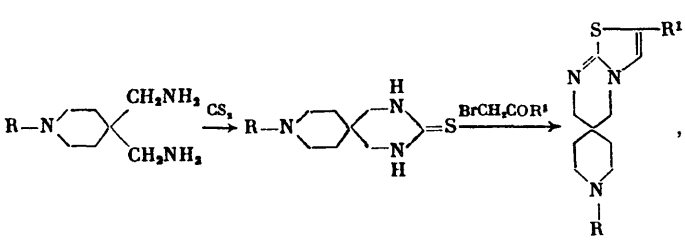
Recently it was shown that 2,4,9-triazaspiro[5.5]undecane-1,3,5-trione derivatives with various substituents on the piperidine nitrogen possess neuroleptic properties.[205,206]

1,3,9-Triazaspiro[5.5]undecane-1,3-dienes have been prepared by interaction of unsaturated nitriles with guanidine.[207] These products are effective for the treatment of Parkinson's disease.



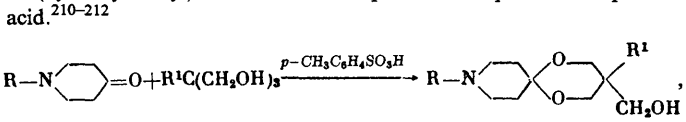
R = methyl, phenylethyl, dimethylaminoethyl; X = OH, NH_2.

The interaction of 1-substituted 4,4-bis(aminomethyl)piperidines with carbon disulphide leads to 9-substituted 2,4,9-triazaspiro-[5.5]undecane-4-thiones, which condense with α-halogenoketones to give spiro[piperidine-4,6-thiazolo[3,2-a]pyrimidines. The latter display antidepressant and thymoanaleptic properties.[208,209]



R = alkyl, aryl, benzyl, furyl, thienyl.

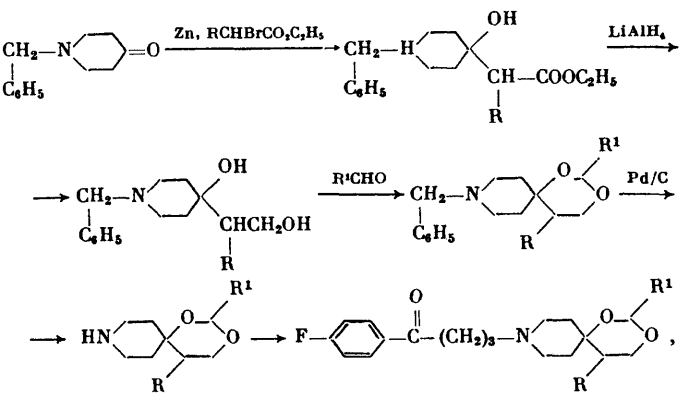
Substituted 1,5-dioxa-9-azaspiro[5.5]undecanes have been synthesised by condensation of 4-piperidones with alkyl-substituted tris(hydroxymethyl)methanes in the presence of *p*-toluenesulphonic acid.[210–212]



R = H, alkyl, aryl, aralkyl, acyl, ethoxycarbonyl, thienylalkyl; R^1 = alkyl.

In the above scheme, 4-piperidone ketals have been used in place of 4-piperidones,[213] and substituted 1,3-dioxanes in place of the triols.[214] Certain of the resulting azaspirodioxanes have been shown to possess tranquillizing activity.[215]

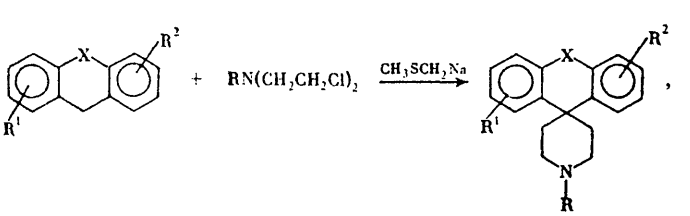
1,3-Dioxa-9-azaspiro[5.5]undecanes have been prepared from 1-benzyl-4-piperidone.[215] Thus, Reformatskii reaction with the latter, followed by reduction of the resulting β-hydroxyesters with $LiAlH_4$, yields the corresponding 1,3-diols, which are cyclised to the desired spiro[piperidine-1,3-dioxanes] with aldehydes:



R = H, alkyl; R^1 = H, alkyl, aryl.

III. Spiro-*N*-heterocycles in which the piperidine ring is spiro-condensed at the four position with condensed heterocycles

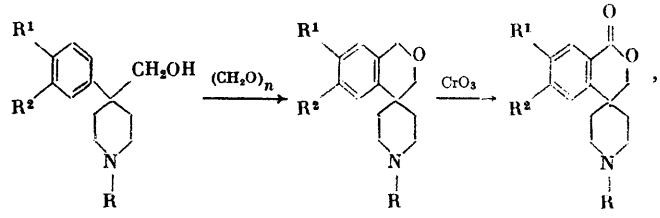
Xanthenes, thioxanthenes and dihydroanthracenes with various substituents in the benzene ring undergo cycloalkylation with bis(2-chloroethyl)amines to give the corresponding 4-spiropiperidines. Certain of these compounds have been used medicinally as analgesics.[216–218]



R = alkyl, aryl, benzyl, alkenyl; R^1 = R^2 = H, OMe, Cl, OH, etc.

References have also been made to the preparation of spiro-[isochroman-4,4'-piperidines] and spiro[isochroman-3,4'-piperidines]. One route to the former involves hydroxymethylation, followed by ring closure of the resulting 4-aryl-4-hydroxymethylpiperidines.[219–223] The starting 4-hydroxymethylpiperidines were obtained by reduction

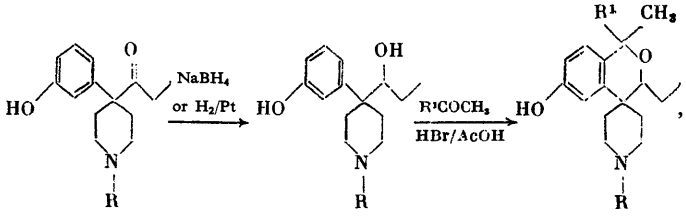
of the corresponding 4-carbalkoxy-derivatives. The spiroisochromans prepared by this method were oxidised to the corresponding spiroisocoumarins with CrO_3.[219,222]



R = alkyl, aryl, benzyl, aralkyl; $R^1 = R^2$ = H, MeO, etc.

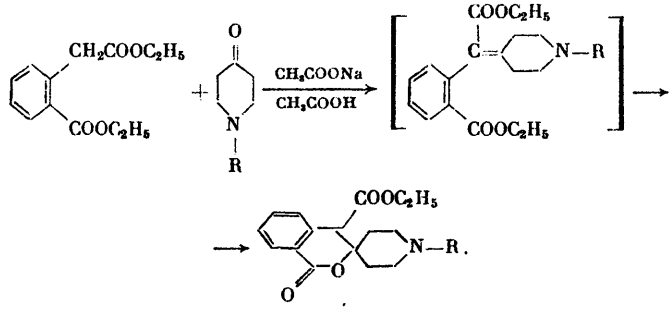
N-Substituted spiro[isochroman-4,4′-piperidines] may also be prepared by reductive *N*-debenzylation, followed by *N*-alkylation.[219]

In an alternative route to these spirocycles, 4-aryl-4-acylpiperidines may be reduced to the corresponding alcohol, and subsequently condensed with alkyl methyl ketones. In this way, derivatives with substituents at the 1 and 4 positions may be prepared.[224]

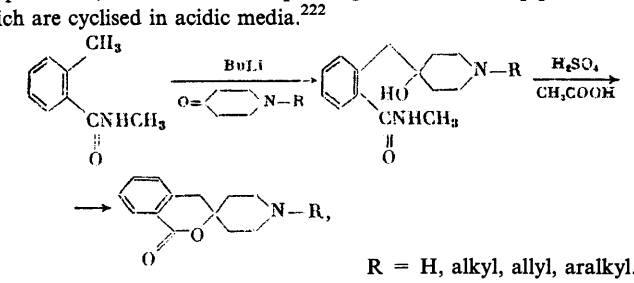


R = alkyl, allyl; R^1 = methyl, ethyl.

Spiro[isochroman-3,4′-piperidines] have been prepared by interaction of diethyl homophthalate with 4-piperidones, followed by cyclisation of the resulting 4-piperidinylidene-derivatives in acidic media.[219]



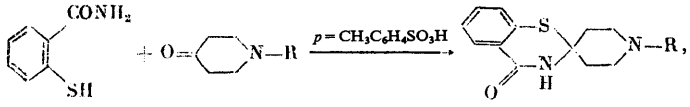
Alternatively, benzylic metallation of *o*-(*N*-methylcarbamyl)-toluene with *n*-butyllithium, followed by treatment with 4-piperidones, affords the corresponding 4-substituted 4-piperidinols, which are cyclised in acidic media.[222]



R = H, alkyl, allyl, aralkyl.

Such spiroisochromans possess analgesic activity.

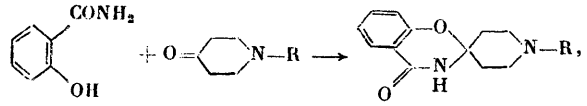
4-Oxospiro[1,3-benzothiazine-2,4′-piperidines] may be obtained by condensation of thiosalicylamide with 4-piperidones.[225]



R = H, butyl, acetyl, benzyl, benzoyl.

These compounds possess sedative, analgesic and hypoglycaemic properties.

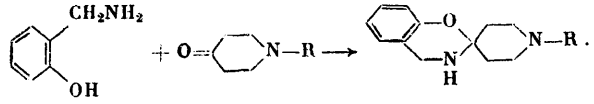
In a similar way, 4-oxospiro[1,3-benzoxazine-2,4′-piperidines] may be prepared by condensation of 4-piperidones with salicylamide.[226]



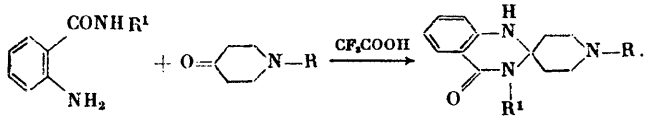
R = H, acetyl, benzyl, ethoxycarbonyl.

It is interesting that these compounds also possess sedative, analgesic, and hypoglycaemic properties.

Spiro[1,3-benzoxazine-2,4′-piperidines] are obtained if *o*-aminomethylphenols are used in place of salicylamides.[227]

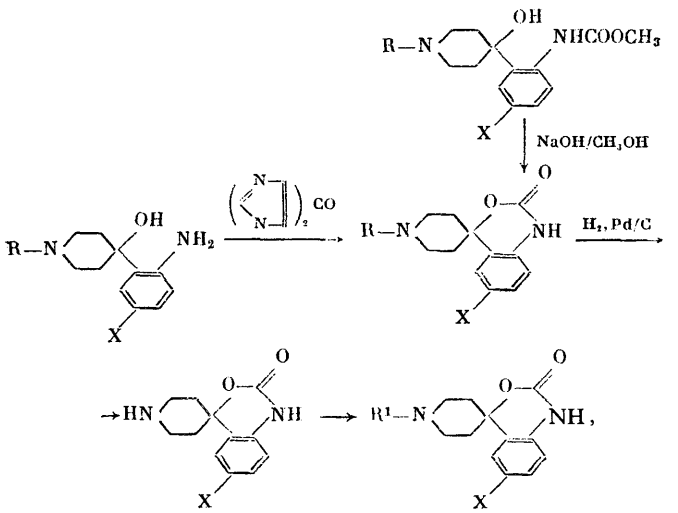


The condensation of anthranilamides with 4-piperidones in the presence of trifluoroacetic acid affords 4-oxospiro[tetrahydroquinazoline-2,4′-piperidines], which display bronchodilator and CNS depressant activity.[228]



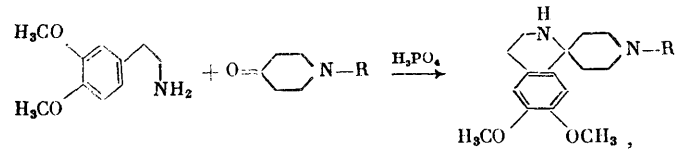
There are two routes to 2-oxospiro[4*H*-3,1-benzoxazine-4,4′-piperidines] based on *N*-substituted 4-hydroxy-4-(2-aminophenyl)piperidines.[229,230] In one of these methods, the latter compounds are converted to *N*-carbomethoxy derivatives with methyl chloroformate, and then cyclised in aqueous ethanolic NaOH. In the other method, the starting 4-piperidinols are cyclised directly with *N*,*N*′-carbonyldiimidazole. A variety of *N*-substituted derivatives may be obtained by reductive cleavage of *N*′-benzyl-2-oxospiro[4*H*-3,1-benzoxazine-4,4′-piperidines], followed by appropriate *N*-alkylation of the *N*-unsubstituted derivatives. These

products possess hypotensive properties and are used medicinally in combination with other drugs.



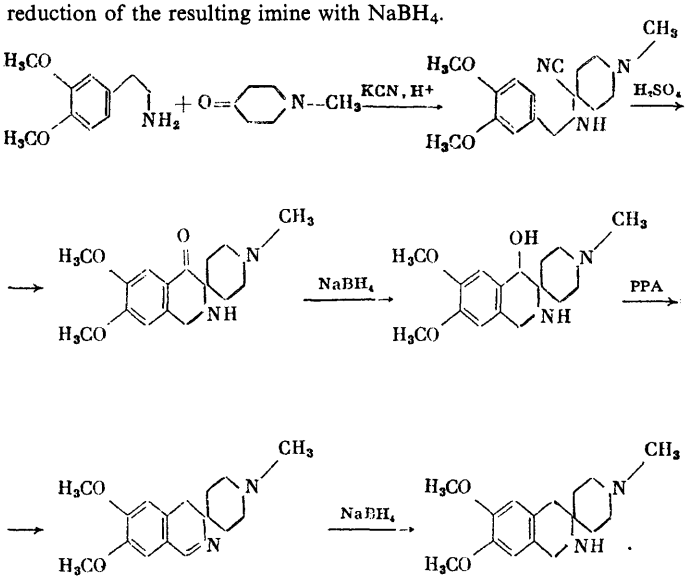
R = H, alkyl, benzyl; R^1 = benzoylbutyl; X = H, Cl.

There are convenient one-step routes to spiro[tetrahydroisoquinoline-1,4′-piperidines] by Pictet-Spengler ring closure of 3,4-dimethoxyphenylethylamine with 4-piperidones in polyphosphoric acid.[231]

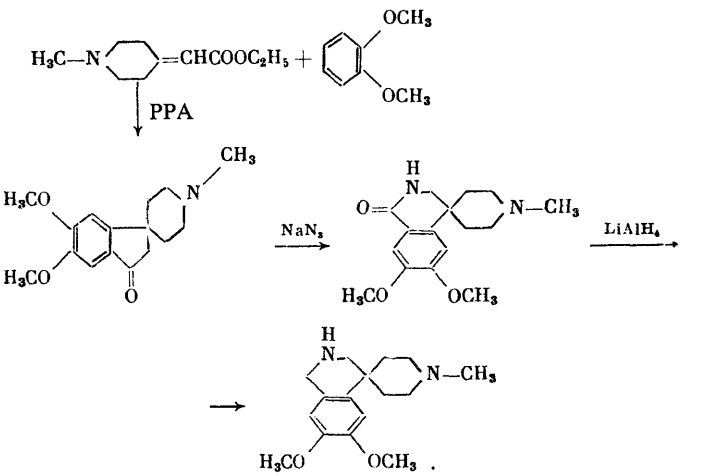


R = methyl, benzyl.

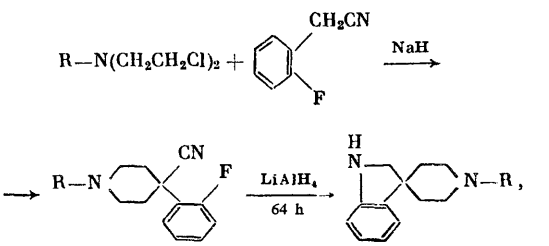
The synthesis of spiro[tetrahydroisoquinoline-3,4′-piperidines] has also been reported.[231] Thus, 3,4-dimethoxyphenylethylamine condenses with 1-methyl-4-piperidone in the presence of KCN to give the corresponding 4-amino-4-cyanopiperidine, which cyclises to 4′-methyl-4-oxo-6,7-dimethoxyspiro[1,2,3,4-tetraisoquinoline-3,4′-piperidine]. The 4-deoxy derivative is obtained by reduction to the corresponding alcohols, followed by dehydration and a second reduction of the resulting imine with $NaBH_4$.



Spiro[isoquinoline-4,4′-piperidines] have been prepared by Schmidt rearrangement of the corresponding spiroindanones, followed by hydride reduction of the resulting lactams.[231] The starting spiroindanones are obtained under Friedel-Crafts conditions by interaction of the corresponding phenolethers with the appropriate 4-carboxymethylenepiperidines or their esters.[232]



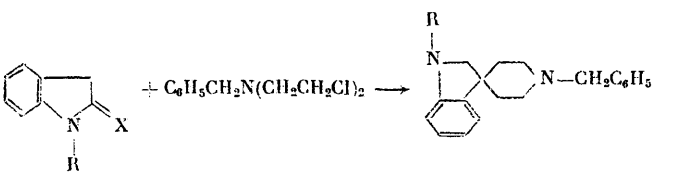
Methods of preparing spiro[indoline-3,4′-piperidines] have been reported in the patent literature.[233,234] These involve condensation of bis(2-chloroethyl)amines with *o*-fluorobenzyl cyanide in the presence of NaH. The resulting 4-cyano-4-(*o*-fluorophenyl)-piperidines are reduced with $LiAlH_4$ over > 60 h, during which time indoline ring closure takes place with liberation of fluoride ion.



R = H, alkyl, CN, acyl, phenyl.

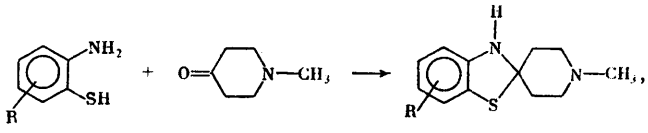
The obtained *N*-substituted indolines are used medicinally as anticonvulsant, antidepressant, and transquillizing drugs.

The preparation of spiro[indoline-3,4′-piperidines] and their 2-oxo-derivatives has been achieved by cycloalkylation of the corresponding indolines with *N*-benzylbis(2-chloroethyl)amine, followed by debenzylation and subsequent *N*-alkylation with various alkyl halides.[235,236] According to the authors, these compounds possess antiarrhythmic, analgesic and antihypertensive activity.



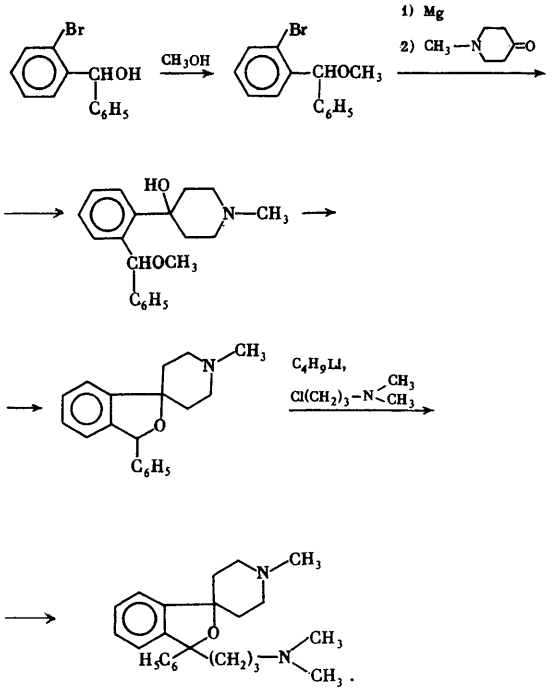
R = H, alkyl, phenyl; X = H_2, O.

o-Aminothiophenols condense with 1-methyl-4-piperidones to give spiro[benzthiazoline-2,4′-piperidines] which possess antiasthmatic properties.[237]

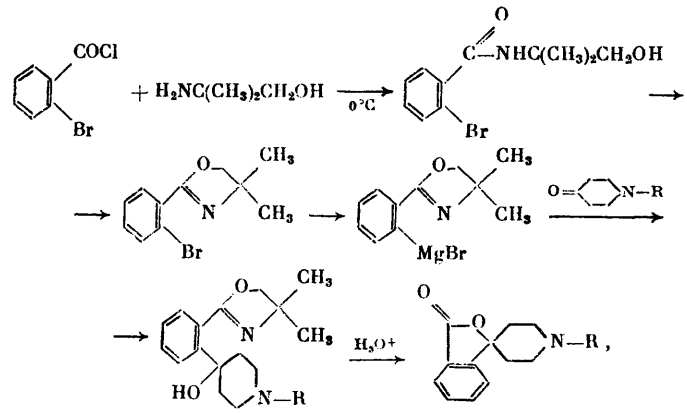


R = H, Cl, Me, MeO.

Spiro[isobenzofuran-1,4-piperidines] are obtained by conversion of *o*-bromobenzhydryl alcohol to the corresponding methyl ether, which, following conversion to the corresponding Grignard reagent, adds to 4-piperidones to give the corresponding 4-aryl-4-piperidinols; the latter are then cyclised to the desired spirocycles, as exemplified below. The resulting 3-phenyl-1,3-dihydrospiro[isobenzofuran-1,4′-piperidine] is converted to the 3-(3-dimethylaminopropyl) derivative by metallation with butyllithium followed by alkylation with 3-dimethylaminopropyl chloride.[238] A number of such spiroisobenzofurans have been discussed in the patent literature.[239]

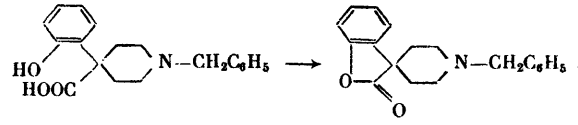


3-Thienyl-1-spiroisobenzofuran analogues have been prepared by the same method and shown to possess tranquillizing and antidepressant activity.[240] The following route is available for preparing 3-oxospiro[isobenzofuran-1,4′-piperidines]. Thus, *o*-bromobenzoyl chloride condenses with 2-amino-2-methylpropanol to give the corresponding benzamide, which undergoes cyclodehydration with $SOCl_2$ to give 2-(2-bromophenyl)-4,4-dimethyl-2-oxazoline. The corresponding Grignard reagent reacts with 4-piperidones to give the corresponding 4-aryl-4-piperidinols which cyclise to the desired spirocycles in acidic media. A number of these compounds possess analgesic, tranquillizing, antidepressant and anticonvulsant activities.[241,242]



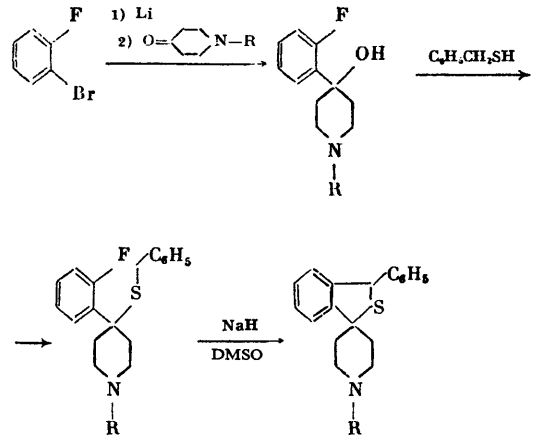
R = methyl, benzyl.

2-Oxospiro[benzofuran-3,4′-piperidines] are formed by cyclisation of *N*-benzyl-4-carboxy-4-(*o*-hydrophenyl)piperidines.[243]



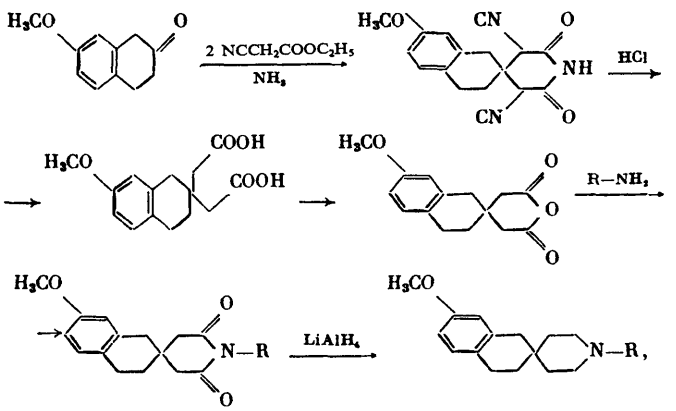
A 3-methylenespiro[benzofuran-2,4′-piperidine] has also been prepared and shown to possess hypotensive properties.[244]

Spiro[benzo[c]thiophene-1,4′-piperidines] have been synthesised as follows. *o*-Fluorophenyllithium, obtained from *o*-fluorobromobenzene by bromine-lithium exchange, condenses with 4-piperidones to give the corresponding 4-aryl-4-piperidinols, which are converted to the desired spirocycles by condensation with benzyl mercaptan followed by ring closure.[245,246]



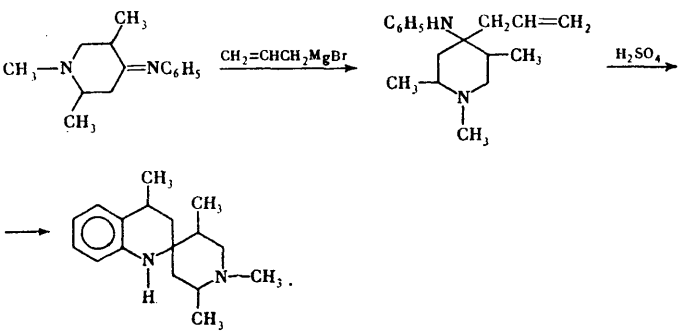
Such spirobenzothiophenes possess anticholinergic properties and are effective antidepressants and sedatives.

Spiro[tetrahydronaphthalene-2,4′-piperidines] have been obtained by conversion of 7-methoxy-2-tetralone to the corresponding Guaveschi's imide, followed by the sequence of steps shown below.[247]

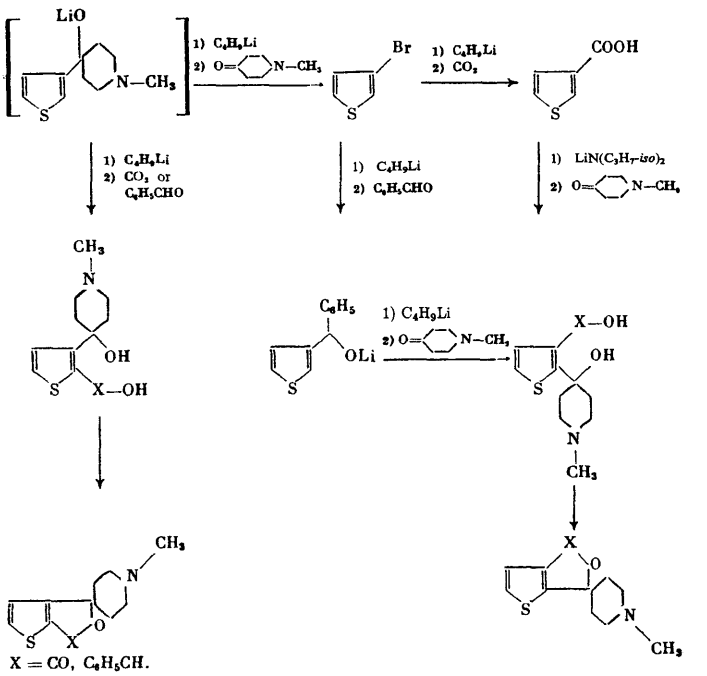


R = dimethylaminopropyl.

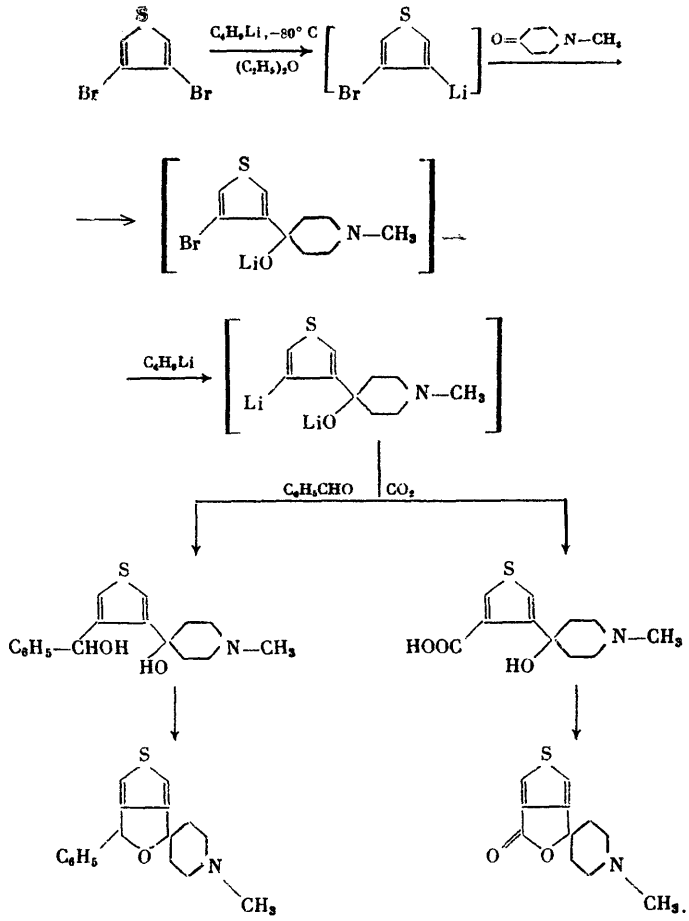
Tetrahydro-1,3,5,7-tetramethylspiro[quinoline-2,4′-piperidine] has been prepared by the high-yielding reaction of 1,2,5-trimethyl-4-phenyliminopiperidine with allylmagnesium bromide, followed by heating the resulting 4-allyl-4-anilinopiperidine in acidic media.[248]



Spiropiperidines having a spiro-condensed thieno[2,3-c]furan ring at the 4-position have been prepared from 3-bromothiophene, which offers scope for incorporating further substituents in the thiophene ring via metallation.[249] Thus, sequential treatment of 3-bromothiophene with butyllithium and 1-methyl-4-piperidone affords the corresponding 4-(3-thienyl)-4-piperidolate, which reacts, sequentially, with a second equivalent of butyllithium and carbon dioxide or benzaldehyde to give the corresponding 2-carboxy- or 2-hydroxyalkylthiophenes. The latter then undergo cyclodehydration as shown below. Alternatively, 3-lithiothiophene reacts with carbon dioxide or benzaldehyde to give the corresponding 3-substituted thiophenes which undergo lithiation at the 2-position. These derivatives then condense with 1-methyl-4-piperidone to give the desired spirocycles.



Piperidines having a spiro-fused thieno[3,4-c]furan ring at the 4-position have been prepared by the above method from 3,4-dibromothiophene. Thus, treatment of the latter with butyllithium at low temperature affords 3-bromo-4-lithiothiophene, which, without isolation, adds to 1-methyl-4-piperidone; the intermediate 4-piperidolate (again without isolation) is further lithiated and the resulting *O,C*-dianion is converted to the desired spirocycle by quenching with benzaldehyde or carbon dioxide, followed by cyclodehydration of the intermediate diol or hydroxyacid in acidic media, as shown below:[250]



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The discovery of spiropiperidine-type biogenic amines and alkaloids has stimulated intense research, notably in the chemistry of azaspiranes having a piperidine ring spiro-fused at the 4-position with various heterocycles containing both nitrogen and other heteroatoms.

Studies of the biological properties of these compounds have shown that they possess a broad spectrum of activity, certain of which have been utilised medicinally. From this survey, one might predict that in the near future these azaspiranes will be used as effective drugs for treating irregularities of the central nervous system.

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