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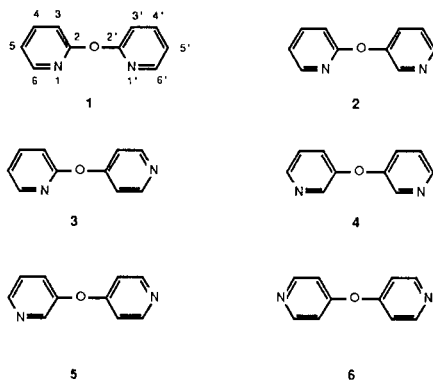
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I. Introduction.

There are six oxybispyridines whose structures are 2,2'-(**1**), 2,3'-(**2**), 2,4'-(**3**), 3,3'-(**4**), 3,4'-(**5**) and 4,4'-(**6**). The term oxybispyridine is in accord with current *Chemical Abstracts* nomenclature although the compounds have also been named as oxydipyridines and dipyriddy ethers.



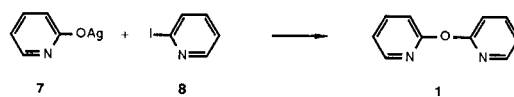
Likewise there are six analogous thiobispyridines, sometimes named as thiodipyridines and dipyriddy sulfides, and six selenobispyridines. The chemistry of oxybispyridines, thiobispyridines, and selenobispyridines has not previously been reviewed. This review provides a thorough coverage of these compounds to the end of 1985 and includes work reported in most chemical journals to mid-1986.

II. Oxybispyridines.

All six of the parent oxybispyridines have been prepared. With the exception of the 3,3'-isomer, which is a liquid, all the oxybispyridines are low melting solids. Some of the properties of the parent compounds are summarized in Table I.

A. 2,2'-Oxybispyridine.

Although the di-*p*-toluenesulfonate of 2,2'-oxybispyridine (**1**) was obtained in 1953 as a by-product of the reaction of picolinic acid 1-oxide with *p*-toluenesulfonyl chloride [1] the first preparation of 2,2'-oxybispyridine (**1**) in 1957 was due to de Villiers and den Hertog [2]. They reacted the silver salt of 2-hydroxypyridine (**7**) with 2-iodopyridine (**8**) to afford a moderate yield of 2,2'-oxybispyridine



(**1**) which was purified by way of its mercuric chloride complex and further characterized as its picrate. This method has been used by others [3]. In a somewhat similar reaction 2-chloro-3,5-dinitropyridine reacted with 2-hydroxy-3,5-dinitropyridine, sometimes as its sodium salt, to afford 3,3',5,5'-tetranitro-2,2'-oxybispyridine [4,5] and modifica-

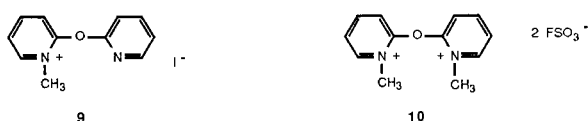
Table 1
Some Properties of Oxybispyridines

Oxybispyridine	Melting Point or Boiling Point (°C)	UV Spectrum (λ max, log ε)	NMR Spectrum (δ, ppm)
2,2'	49-50 [a]	216, 264 (4.0, 3.9) [a] [b], 262 (3.85) [c] [d]	6.95-7.13 (m, 4H), 7.56-7.88 (m, 2H), 8.20-8.32 (m, 2H) [c] [e]
2,3'	30-32 [a] 34-35 [f]	214, 264 (4.0, 3.8) [a] [b]	—
2,4'	40 [g]	225, 255 sh, 262, 266 sh (4.07, 3.64, 3.67, 3.66) [d] [g]	6.95-7.30 (m, 4H), 7.65-7.95 (m, 1H), 8.23-8.35 (d, 1H), 8.51-8.62 (d, 2H) [e] [g]
3,3'	140-141/0.1 mm [h]	216, 268, 274, (4.30, 4.07, 4.02) [d] [h]	7.3-7.4 (m, 4H), 8.4-8.5 (m, 4H) [e] [h]
3,4'	48-50 [i]	—	8.56 (d, 4H), 7.56 (m, 2H), 7.08 (d, 2H) [i]
4,4'	40-42 [j] 67 [i] 61-62 [k]	227 (4.04) [d] [k]	7.37 (d, 4H), 8.57 (d, 4H) [j], 7.18 (d, 4H), 8.42 (d, 4H) [i] 6.95-7.05 (d, 4H), 8.56-8.66 (d, 4H) [e] [k]

[a] Ref 2. [b] Aqueous ethanol. [c] Ref 3. [d] Ethanol. [e] Deuteriochloroform. [f] Ref 22. [g] Ref 30. [h] Ref 31. [i] Ref 34. [j] Ref 37. [k] Ref 38.

tions of this procedure have subsequently been used to prepare a number of substituted 2,2'-oxybispyridines [6]. Another route to 2,2'-oxybispyridine involves the dehydration of 2-hydroxypyridine in benzene solution at 170° under pressure [7,8]. Some partly reduced derivatives of 2,2'-oxybispyridine have been formed by the coupling of various 1-benzylpyridinium salts with alkali [9-11] and have possibly been formed as by-products in an alkaloid synthesis [12].

Some reactions of 2,2'-oxybispyridine have been reported. As expected 2,2'-oxybispyridine forms a monomethiodide **9** with methyl iodide [3] and a diquaternary salt, 1,1'-dimethyl 2,2'-oxybispyridinediium bisfluorosulfonate (**10**) with methyl fluorosulfonate [3]. The di-cation of **10** is



also formed by reaction of 1-methyl-2-pyridone with trifluoromethanesulfonic anhydride followed by heating [13,14]. The diquaternary salt (**10**) is reduced polarographically in aqueous solution by a one electron transfer to the corresponding radical cation at a potential (E_0) of -0.71V [3]. The mono-cation (**9**) is also formed from 2-fluoro-1-methylpyridinium *p*-toluenesulfonate and 2-hydroxypyridine during a high voltage paper electrophoretic characterization of hydroxy compounds [15].

Some 6-methyl substituted 2,2'-oxybispyridines have been converted to the 1-oxides with hydrogen peroxide. The oxides on treatment with acetic anhydride afforded the 6-acetyloxymethyl-2,2'-oxybispyridines which on hydrolysis gave the 6-hydroxymethyl derivatives. These were subsequently esterified with several cyclopropanecarboxylic acids or etherified with a variety of β -hydroxyethylbenzenes to produce insecticidal esters and ethers respectively [6].

In spectral studies the mass spectral fragmentation pattern of 2,2'-oxybispyridine (**1**) has been fully elucidated. The base peak is due to the molecular ion at mass 172 and the principal fragmentations involve loss of H^+ , C_2HO^+ , and CO as well as rupture of the central bond [16]. Mass spectrometry has been used to identify 2,2'-oxybispyridine, and a number of substituted 2,2'-oxybispyridines as products from the aprotic decomposition of 2-aminopyridines in the presence of isoamyl nitrite [17].

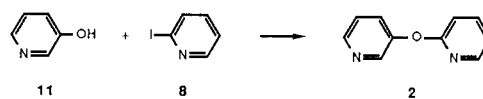
Theoretical calculations by the MIM method have been applied to the UV spectrum of 2,2'-oxybispyridine (**1**) and to its dipole moment to obtain information on the conformation of the molecule [18].

In practical applications 2,2'-oxybispyridine has been advocated as a suitable ligand for cobalt carbonyl for the

formation of a catalyst useful in the hydroformylation of olefins [7,8] and partly hydrogenated 2,2'-oxybispyridines are included in a patent as co-catalysts in the polymerization of caprolactam [9]. Partly hydrogenated 2,2'-oxybispyridines have also been patented as brighteners in electroplating processes [10,11,20] and have been postulated as species involved in the brightening action on electroplated zinc of quaternary pyridine salts [21].

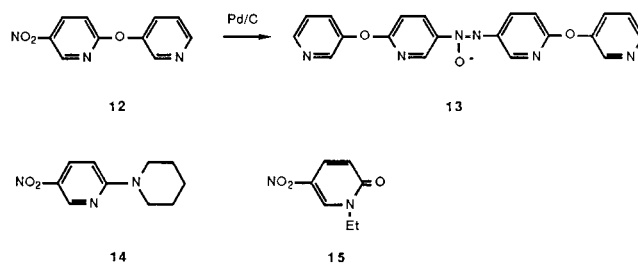
B. 2,3'-Oxybispyridine.

In an analogous way to the preparation of 2,2'-oxybispyridine, 2,3'-oxybispyridine (**2**) can be prepared by reaction of 3-hydroxypyridine (**11**), or a salt thereof, with a 2-halopyridine such as 2-iodopyridine (**8**) [2,22]. 2,3'-Oxybispyridine (**2**) was sometimes purified as its mercuric chloride complex and further characterized as the picrate.



This route has also been applied to the synthesis of some substituted 2,3'-oxybispyridines [6,22-24]. Another route to 2,3'-oxybispyridine involves reaction of pyridine 1-oxide with 2-pyridyl *p*-toluenesulfonate although several other products are usually formed as well in the process [2]. Other related methods have used *p*-toluenesulfonyl chloride [25] or 2-bromopyridine [26,27] instead of 2-pyridyl *p*-toluenesulfonate. Heating 2-pyridyl *p*-toluenesulfonate alone also gives a low yield of 2,3'-oxybispyridine [2]. In unusual routes to substituted 2,3'-oxybispyridines it has been found that 1-(5-nitro-2-pyridyl)-3-hydroxypyridinium chloride on pyrolysis in a mass spectrometer affords 5-nitro-2,3'-oxybispyridine [28] and in a related process 1-(5-nitro-2-pyridyloxy)-4,6-diphenyl-2-pyridone on photolysis affords 5-nitro-2'-hydroxy-4',6'-diphenyl-2,3'-oxybispyridine [29].

Several reactions of 2,3'-oxybispyridines have been described. Nitration of 2,3'-oxybispyridine (**2**) affords 5-nitro-2,3'-oxybispyridine (**12**) [22], the nitro group of which is reduced to amino by standard procedures [22,23]. Catalytic reduction of 5-nitro-2,3'-oxybispyridine, however, with palladium charcoal affords 6,6'-bis(3-pyridyloxy)-3,3'-azoxyxyridine (**13**) several further transformations of which have been reported [22]. The reactive



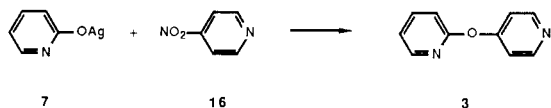
2-(3'-pyridyloxy) group of 5-nitro-2,3'-oxybispyridine (**12**) is readily replaced by piperidine to afford compound (**14**) while reaction of 5-nitro-2,3'-oxybispyridine (**12**) with sodium ethoxide affords 1-ethyl-5-nitro-2-pyridone (**15**) [22]. Some 6-methyl substituted 2,3'-oxybispyridines, like their 2,2'-oxybispyridine counterparts, have been converted to 6-hydroxymethyl analogues which were esterified with several cyclopropanecarboxylic acids or etherified with a variety of β -hydroxyethylbenzenes to give insecticidally active products [6].

In spectral studies, proton and ^{13}C nuclear magnetic resonance spectra of some substituted 3-nitro-2,3'-oxybispyridines have been described [24]. As with 2,2'-oxybispyridine theoretical calculations by the MIM method have been applied to 2,3'-oxybispyridine [18].

In practical applications 2,3'-oxybispyridine is claimed to have psychotropic and bactericidal properties [27]. 5-Nitro-2,3'-oxybispyridine (**12**) has some tuberculostatic activity [23].

C. 2,4'-Oxybispyridine.

2,4'-Oxybispyridine (**3**) has been obtained along with 1-(4-pyridyl)-4-pyridone by heating 4-nitropyridine (**16**) with the silver salt of 2-hydroxypyridine (**7**) [30]. Some substituted 2,4'-oxybispyridines have recently been synthesized by reacting a 2-halopyridine with 4-hydroxypyridines

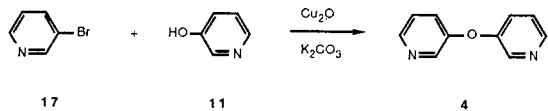


in the presence of base [6]. 6-Methyl substituted 2,4'-oxybispyridines have been converted to 6-hydroxymethyl derivatives by a route analogous to that described for the corresponding 2,2'-oxybispyridines. The 6-hydroxymethyl-2,4'-oxybispyridines likewise were converted to a number of insecticidally active esters and ethers [6].

In the mass spectrum of 2,4'-oxybispyridine (**3**) the base peak is due to the M-1 ion with the molecular ion at mass 172 giving a peak amounting to 80% of the intensity of the base peak. Fragmentations from the molecular ion involve loss of HCN, CO, CO + C₂H₂ and CO + HCN [30]. The only other publication on 2,4'-oxybispyridine records a theoretical treatment by the MIM method [18].

D. 3,3'-Oxybispyridine.

3,3'-Oxybispyridine (**4**) has been obtained by reaction of 3-bromopyridine (**17**) with 3-hydroxypyridine (**11**) under pressure in the presence of potassium carbonate and cuprous oxide [31]. In a related synthesis 3-bromopyridine



1-oxide reacted with the potassium salt of 3-hydroxypyridine in the presence of copper to afford 3,3'-oxybispyridine-1-oxide which was deoxygenated with iron in acetic acid to give 3,3'-oxybispyridine (**4**) [32]. Recently another similar route to 3,3'-oxybispyridine was described. Reaction of 3-fluoro-4-nitropyridine 1-oxide with 3-hydroxypyridine gave 4-nitro-3,3'-oxybispyridine 1-oxide which was converted to 3,3'-oxybispyridine by standard reduction and deamination procedures [33].

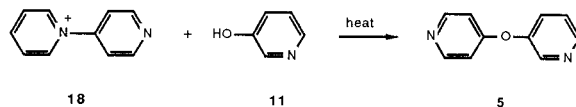
In reactions of 3,3'-oxybispyridine the diquaternary salts 1,1'-dimethyl 3,3'-oxybispyridinediium diiodide and 1,1'-diethyl 3,3'-oxybispyridinediium diiodide are formed from 3,3'-oxybispyridine (**4**) by reaction with excess methyl iodide and ethyl iodide respectively. The former salt is reduced polarographically in aqueous solution by a one electron transfer to the corresponding radical cation at an E₀ value of -0.81V [31]. 3,3'-Oxybispyridine 1-oxide is converted, as expected, to the 1,1'-dioxide with hydrogen peroxide in acetic acid [32].

In the mass spectrum of 3,3'-oxybispyridine (**4**) the base peak at mass 172 is due to the molecular ion. The M-1 ion accounts for a peak of only 4% of the intensity of the base peak. The main fragmentations from the molecular ion involve either loss of CO + HCN or arise from rupture of the central bonds [31]. Theoretical studies of 3,3'-oxybispyridine by the MIM method have been reported [18].

In practical applications 3,3'-oxybispyridine, the 1-oxide and the 1,1'-dioxide have been found to have activity in influencing learning or memory in mice [32].

E. 3,4'-Oxybispyridine.

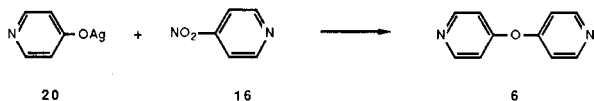
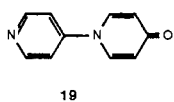
The only synthesis of 3,4'-oxybispyridine (**5**) involves heating 1-(4-pyridyl)-pyridinium chloride (**18**) with 3-hydroxypyridine (**11**) [34]. It was characterized as the picrate.



Theoretical studies of 3,4'-oxybispyridine by the MIM method have been reported [18].

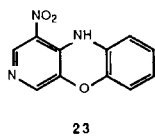
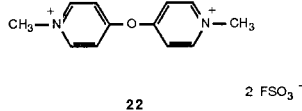
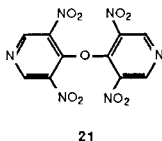
F. 4,4'-Oxybispyridine.

4,4'-Oxybispyridine (**6**) was thought to have been prepared in 1930 by heating 4-acetyloxy pyridine [35] but the product was later found to be instead 1-(4-pyridyl)-4-pyridone (**19**) [36]. Authentic 4,4'-oxybispyridine was not synthesised until 1976 when it was found to be formed in very low yield (4%) by the reaction of pyridine 1-oxide with trichloroacetyl chloride. It was characterized as the picrate [37]. 4,4'-Oxybispyridine is formed in similar low yield by reaction of 1-(4-pyridyl)-pyridinium chloride (**18**) with 4-hydroxypyridine [34]. A better more recent method of formation of 4,4'-oxybispyridine, although still only in moderate



yield, involves heating the silver salt of 4-hydroxypyridine (**20**) with 4-nitropyridine (**16**) [38]. A substituted 4,4'-oxybispyridine, namely 3,3',5,5'-tetranitro-4,4'-oxybispyridine (**21**) has been prepared by dehydration of 3,5-dinitro-4-hydroxypyridine with *p*-toluenesulfonyl chloride in the presence of *N,N*-diethylaniline [39].

In reactions of 4,4'-oxybispyridine, it forms the diquaternary salt 1,1'-dimethyl-4,4'-oxybispyridinediium bis-(fluorosulfonate) (**22**) with methyl fluorosulfonate. The diquaternary salt (**22**) is reduced polarographically in



aqueous solution by a one electron transfer to the corresponding radical cation at an E_0 value of -0.80 V [40]. The tetranitro derivative (**21**) reacts with *o*-aminophenol to form the phenoxazine (**23**) and with *o*-aminothiophenol to

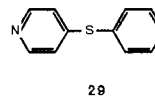
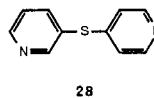
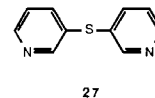
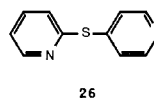
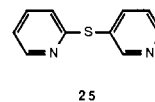
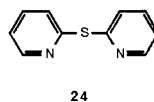
afford the analogous phenothiazine. The tetranitro derivative (**21**) is hydrolysed to 3,5-dinitro-4-hydroxypyridine with alkali [39].

In spectral studies, the mass spectrum of 4,4'-oxybispyridine (**6**) shows that the base peak is due to the molecular ion at mass 172. The *M*-1 ion accounts for a peak of 24% of the intensity of the base peak. Other fragmentation routes involve loss of CO, HCN, $\text{C}_2\text{H}_2\text{N}$ and C_2HO as well as rupture of the central bonds [41].

Like the other oxybispyridines 4,4'-oxybispyridine has been the subject of a theoretical study by the MIM method [18].

III. Thiobispyridines.

All of the parent thiobispyridines have been synthesised. Some of their properties are summarized in Table 2.



2,2'-Thiobispyridine.

2,2'-Thiobispyridine (**24**) was first synthesized in 1937 by reacting 2-bromopyridine with cupric thiocyanate in methanol. It was isolated as the dihydrobromide from

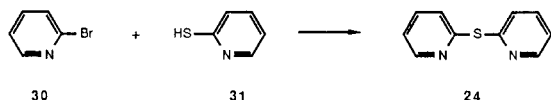
Table 2

Some Properties of Thiobispyridines

Thiobispyridine	Melting Point or Boiling Point (°C)	UV Spectrum (λ max, log ϵ)	NMR Spectrum (δ , ppm)
2,2'	172-173/9 mm [a] 148/1 mm [d]	—	8.56 (d, 2H), 7.62 (m, 4H), 7.24 (m, 2H) [c] [d]
2,3'	oil [e]	—	—
2,4'	oil [c]	—	8.66 (d, 2H), 8.17-7.25 (m, 6H) [c] [d]
3,3'	35 [f] 36 [g] 140/0.5 mm [g]	195, 211 sh, 249, 278 sh, (4.21, 4.04, 3.94, 3.76) [g] [h]	7.12-7.35 (m, 2H), 7.5-7.75 (d, 2H), 8.45-8.65 (m, 4H) [g] [i]
3,4'	oil [e]	—	—
4,4'	155/1.5 mm [j] 71 [j] 69 [k] 72 [e] [l]	—	8.66 (d, 4H), 7.33 (d, 4H) [c] [d]

[a] Ref 45. [b] Ref 68. [c] Ref 79. [d] Carbon tetrachloride. [e] Ref 78. [f] Ref 147. [g] Ref 146. [h] Water. [i] Deuteriochloroform. [j] Ref 155. [k] Ref 172. [l] Ref 156.

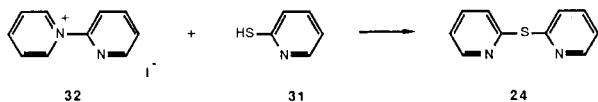
which the parent compound was obtained by treatment with aqueous sodium carbonate. It is a yellow oil [42]. This method has been utilized subsequently [43,44]. Another method of preparing 2,2'-thiobispyridine (**24**) involves reacting 2-bromopyridine (**30**) with pyridine-2-thiol (**31**) in



hot benzene [45]. It was characterized as the dihydrobromide and picrate. This method, sometimes with modifications has been used subsequently [e.g. 46,47]. It has also been utilized for the synthesis of various substituted 2,2'-thiobispyridines from appropriate pyridine-2-thiols and 2-halopyridines [24,45,48-65] and for the synthesis of 2,2'-thiobispyridine 1-oxides [66,67].

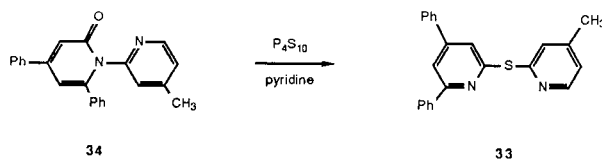
A closely related method, which has been patented, involves the reaction of a 2-halopyridine with sodium sulfide or other alkali metal sulfides whereby 2,2'-thiobispyridine (**24**) is obtained [68]. This method had been used earlier for the synthesis of 5,5'-dinitro-2,2'-thiobispyridine from 2-chloro-5-nitropyridine and sodium sulfide [69] and has been applied to the synthesis of various substituted 2,2'-thiobispyridines [70-72]. It has recently been shown that yields are improved by use of phase transfer catalysts [73]. Potassium hydrogen sulfide [51,58], thiourea [4,74-76], thioacetamide [76], diethyl phosphothioates [77] and 2-mercaptobenzimidazole [62] may be used instead of sodium sulfide.

2,2'-Thiobispyridine (**24**) is also obtained in about 80% yield by heating pyridine-2-thiol (**31**) alone at 240° [78]. In another route to 2,2'-thiobispyridine, although only in



moderate yield, 1-(2-pyridyl)pyridinium iodide (**32**) was heated with pyridine-2-thiol (**31**) [79,80].

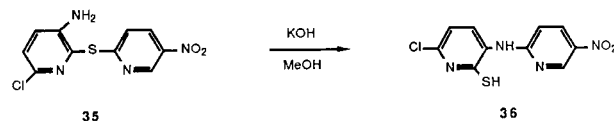
Some partly reduced derivatives of 2,2'-thiobispyridine have been formed by the coupling of various 1-benzylpyridinium salts with hydrogen sulfide [10,11]. Substituted 2,2'-thiobispyridines such as compound **33** are formed



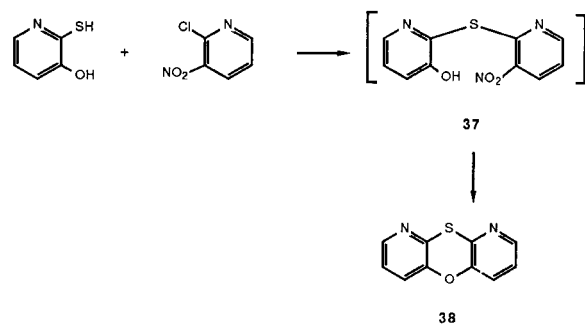
from 1-pyridyl-2-pyridones (e.g. **34**) by treatment with P_4S_{10} in pyridine or by thermolysis of the analogous 1-pyridyl-2-pyridinethione (**34**, S for O) [81,82].

Many reactions of 2,2'-thiobispyridines have been studied. Several standard transformations of substituents have been applied in 2,2'-thiobispyridines. Nitro to amino [49,52,54,60,61,64,69,70,72,83], amino to acylamino and alkylamino [49,54,56,58-61,69,72] and amino to sulfonyl chloride and sulfonamide [71] have been reported and diazotised amino groups have been used in coupling reactions [52]. Amino groups have also been converted to phthalimide derivatives with phthalic anhydride [72]. Some diamino substituted 2,2'-thiobispyridines and their sulfoxides as well as diamino substituted 2,2'-sulfonylbispyridines give polymers with, for example, pyromellitic anhydride and benzophenonetetracarboxylic acid dianhydride [72, 84-86]. The electrical properties of some of these polymers have recently been modified using metal ions [87].

There has been considerable interest in the Smiles rearrangement of appropriately substituted aminonitro-2,2'-thiobispyridines. Thus 3-amino-6-chloro-5'-nitro-2,2'-thiobispyridine (**35**) rearranges to 5-nitro-2'-mercapto-6'-chloro-2,3'-iminobispyridine (**36**) in methanolic potassium hydroxide [55] and several closely related transformations



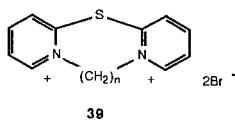
have been described some of which occurred by heat alone without the use of alkali [56-61]. The rearrangement also occurs in acid conditions [60,61,64]. The presence of a nitro group is not always essential for the rearrangement to take place. For example, 3-amino-3'-methyl-2,2'-thiobispyridine rearranges to 3-methyl-2'-mercapto-2,3'-iminobispyridine and other similar rearrangements not requiring a nitro group were effected [64]. Sometimes the pyridylthio group is displaced with methanolic potassium hydroxide. For example, 3-amino-6-ethoxy-5'-nitro-2,2'-thiobispyridine affords *inter alia* 2-methoxy-5-nitropyridine [57] and other similar displacements, some in acid conditions, have been reported [59,60]. With 3-amino (or acetamido)-3'-nitro-2,2'-thiobispyridines the Smiles rearrangement product may ring close to afford dipyridothiazines [56,58,



59,61]. In another ring closure reaction the condensation of 2-mercapto-3-pyridinol (as its sodium salt) with 2-chloro-3-nitropyridine affords the intermediate hydroxynitro-2,2'-thiobispyridine (**37**) which immediately forms the dipyridooxathiin (**38**) [24].

In reactions involving the sulfur bridge 2,2'-thiobispyridine and some substituted derivatives have been oxidized to the corresponding sulfones (2,2'-sulfonylbispyridines) with dichromate [43,48,69,70], hydrogen peroxide [49,55,59,72,88] and permanganate [54,55,59,83]. The sulfoxide of 2,2'-thiobispyridine has also been mentioned in the literature but no details of its preparation were given [89]. The sulfoxide of 5,5'-diamino-2,2'-thiobispyridine has, however, been obtained by treatment of 5,5'-bis(acetylamino)-2,2'-thiobispyridine with hydrogen peroxide for a short time followed by hydrolysis of the acetylamino groups [72]. In an interesting rearrangement reaction the sulfoxide of 2,2'-thiobispyridine (2,2'-sulfinylbispyridine) forms 2,2'-bipyridine on reaction with ethylmagnesium bromide in tetrahydrofuran [90].

In reactions on nitrogen a monoquaternary salt of 2,2'-thiobispyridine has been prepared from methyl iodide in acetone [45] while 1,1'-dialkyl diquaternary salts have been obtained by prolonged heating of 2,2'-thiobispyridine with methyl iodide and ethyl bromide [91,92]. Bridged diquaternary salts (**39**; $n = 1$) and (**39**; $n = 2$) are formed with dibromomethane [92,93] and dibromoethane



[92,94] respectively. The diquaternary salts are reduced in aqueous solution at potentials (E_0) of about -0.36 to -0.49 V to unstable radical cations by the uptake of one electron [91,92]. As a close relative of 2,2'-bipyridine, 2,2'-thiobispyridine, as expected, forms complexes with a variety of metal ions. Copper [44,95], cobalt [44,96], zinc [44], nickel [44], lanthanum [97,98] and uranium [99-102] complexes have been described. 2,2'-Sulfonyl-bispyridine also forms complexes with copper ions [44].

In miscellaneous reactions of 2,2'-thiobispyridine it has been found that reaction of 2,2'-thiobispyridine with sulfur at $160-170^\circ$ affords 2-methylthio-pyridine in nearly 60% yield after methylation of the product with dimethyl sulfate [103] while reaction of 2,2'-thiobispyridine with diphenyl disulfide at 180° in a sealed tube affords phenyl 2-pyridyl disulfide, 2,2'-dithiobispyridine and phenyl 2-pyridyl sulfide. Related reactions were also reported [65]. In a somewhat similar reaction 2,2'-thiobispyridine reacts with phenol to afford pyridine-2-thiol and phenyl 2-pyridyl ether by the aromatic ipso substitution by the phenoxy group [104].

In spectral studies the mass spectrum of 2,2'-thiobispyri-

dine shows that the base peak is due to the M-1 ion. The principal fragmentation routes involve loss of H, CS, CHCS and HCN from the molecular ion, which gives a peak of 36% of the intensity of the base peak, and CS, HCN and S from the M-1 species. Rupture of the central bonds is also an important disintegration pathway [105]. In the mass spectrum of 3-nitro-6-(2-pyridylthio)-2,2'-thiobispyridine the base peak is due to a species at mass 296 obtained by loss of NO_2 from the molecular ion [106]. Infrared and Raman spectra of 2,2'-thiobispyridine and 2,2'-sulfonylbispyridine have been taken and the peaks assigned [107]. The Fourier transform proton magnetic resonance spectrum of 2,2'-thiobispyridine has also been measured and analysed [46] and ^{13}C and proton nuclear magnetic resonance spectroscopy of some 3-nitro-2,2'-thiobispyridines [24] have been useful, along with X-ray crystallography, in elucidating sulfur-nitro interactions [108]. Photoelectron spectra of 2,2'-thiobispyridine and some relatives have been reported and treated theoretically [109].

From gas electron diffraction studies it has been deduced that the angle C-S-C in 2,2'-thiobispyridine is about 104° [110]. Further work has been reported on electron diffraction of 2,2'-thiobispyridine [111]. The electronic spectrum of 2,2'-thiobispyridine has been the subject of quantum chemical calculations [112]. Nitro substituted 2,2'-thiobispyridines have also been the subject of quantum chemical treatment [113]. From calculations applied to the ultra-violet and infra-red spectra of 2,2'-sulfonylbispyridines it has been concluded that the pyridine ring planes are perpendicular to the plane of C-S-C and the nitrogen atoms are anti to each other [114].

The dipole moment of 2,2'-thiobispyridine has been determined as 3.50 D in benzene solution [46]. Values for nitro substituted 2,2'-thiobispyridines [113] and for 2,2'-sulfonylbispyridines have also been reported [114,115]. Atomic refractivities of 2,2'-thiobispyridine and some derivatives have been measured [116].

In practical applications there has been much interest in the biological activity of 2,2'-thiobispyridines. The parent compound 2,2'-thiobispyridine shows pronounced activity against streptococcus infections of rabbits [42] and has some antithyroid activity [117,118]. It has shown activity in various anti-bacterial, anti-fungal and antitumour tests [119] and has been patented as an ingredient of anti-dandruff creams and shampoos [120]. 2,2'-Thiobispyridine has also been patented as a flavouring agent for foodstuffs [121-127]. Various nitro and amino substituted 2,2'-thiobispyridines have been widely studied. They have been shown to have anti-tumour activity [88] and to affect the metabolism of tumours [128]. They are active as anti-tuberculosis agents [129], as anti-malarials [130], as anti-thyroid agents [118] and as anti-bacterials [131] and have been tested for anti-mitotic [63,132] and anti-streptococcal [70] activity. They have been patented as bactericides, mi-

crobiocides, fungicides, herbicides and dye intermediates [49,80]. Some sulfonamido substituted 2,2'-thiobispyridines inhibit carbonic anhydrase and have diuretic activity [71].

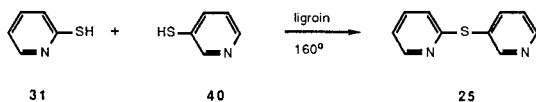
Diquaternary salts of 2,2'-thiobispyridine have been tested as herbicides but they are inactive [91,92]. Some halogenated 2,2'-thiobispyridine 1-oxides, however, are claimed to be antidotes for haloacetanilide herbicides [66] and nitro halogeno-2,2'-thiobispyridine-1-oxides have been patented as fungicides [67]. 2,2'-Thiobispyridine-1,1'-dioxide also shows anti-fungal and anti-bacterial activity and is inhibitory to growth in plants [133].

2,2'-Sulfonylbispyridine and some of its nitro and amino substituted derivatives are also biologically active. They show anti-bacterial [43,70,115], anti-streptococcal [134] and anti-malarial [130] activity and have been patented as bactericides, microbiocides and dye intermediates [49]. 5,5'-Dinitro-2,2'-sulfonylbispyridine was however, inactive in anti-tumour tests [88]. Some methyl substituted 2,2'-thiobispyridines and 2,2'-sulfonylbispyridines as well as the corresponding sulfoxides have recently been synthesised for the purpose of pharmacological evaluation [135].

In other areas of application 2,2'-thiobispyridine has been patented as a compound useful in assisting the side chain chlorination of phenoxytoluenes [136] and is included in patents as a component of a polymer mix for adding to lubricating oils to improve their viscosity [137,138]. Partly hydrogenated 2,2'-thiobispyridines have been patented as brighteners in electroplating processes [10,11,20].

B. 2,3'-Thiobispyridine.

2,3'-Thiobispyridine (**25**) is formed in 90% yield by heating 2-mercaptopyridine (**31**) with 3-mercaptopyridine



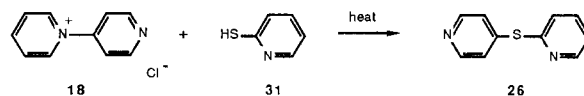
(**40**) at 160° in ligroin until evolution of hydrogen sulfide ceases. It is an oil but no physical constants were recorded. It forms a picrate [78]. In synthesis of substituted 2,3'-thiobispyridines condensation of 2-amino-5-iodopyridine with 2-mercaptopyridine in the presence of sodium methoxide afforded 6'-amino-2,3'-thiobispyridine. This compound served as precursor for the synthesis of an imidazopyridine derivative which was patented as an anthelmintic and fungicide [139]. Similarly, condensation of 3-mercaptopyridine formed *in situ* with 2-chloro-3-nitropyridine gave 3-nitro-2,3'-thiobispyridine, the nitro group of which was converted to amino by standard methods [64].

5-Nitro-2,3'-sulfonylbispyridine and 5-amino-2,3'-sulfonylbispyridine have anti-bacterial activity [140] and the former also shows anti-tumor activity [88] but the synthesis

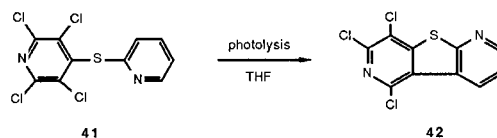
of neither compound was disclosed.

C. 2,4'-Thiobispyridine.

2,4'-Thiobispyridine (**26**) was prepared in 80% yield in 1980 by heating 1-(4-pyridyl)pyridinium chloride (**18**) with pyridine-2-thiol (**31**). The reaction was applied also to the synthesis of methyl and ethyl substituted 2,4'-thiobispyridines [79,80]. In syntheses of other 2,4'-thiobispyridines,



pyridine-4-thiol, sometimes as its potassium salt, reacted, for example, with 2-chloro-5-nitropyridine to afford 5-nitro-2,4'-thiobispyridine [141] and several similar syntheses of nitro substituted 2,4'-thiobispyridines have been reported [55-57,141,142]. Similarly, pyridine-2-thiol reacted with 4-chloro-3-nitropyridine to give 3'-nitro-2,4'-thiobispyridine [64]. In an interesting example, analogous to the corresponding reaction already described in the 2,2'-thiobispyridine series, 3-nitro-4-chloropyridine reacted with 2-mercapto-3-hydroxypyridine, as its sodium salt, to give 3-hydroxy-3'-nitro-2,4'-thiobispyridine which immediately ring closed to a dipyridooxathiin [24]. In a similar reaction 4-bromotetrachloropyridine likewise reacted with pyridine-2-thiol to form 2',3',5',6'-tetrachloro-2,4'-thiobispyridine (**41**), which on photolysis in tetrahydrofuran lost hydrogen chloride to give the trichlorodipyridothiophen (**42**). Pentachloropyridine and some polymeric material were also formed in the process [143].



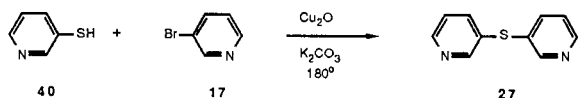
In reactions of 2,4'-thiobispyridines several standard substituent transformations have been recorded. Nitro has been converted to amino [64,141,144] and amino to acetamido [56], while the sulfur bridge has been converted to sulfone with permanganate [141]. Like their 2,2'-thiobispyridine counterparts some appropriately substituted aminonitro 2,4'-thiobispyridines participate in the Smiles rearrangement [56,57] although the presence of a nitro group is not essential for the rearrangement to take place [64]. Displacement reactions may also occur. Thus 5-nitro-3'-amino-2,4'-thiobispyridine on reaction with methanolic potassium hydroxide followed by methylation affords *inter alia* 3-amino-4-methylthiopyridine [57].

In practical applications, 2,4'-thiobispyridines have been patented as bactericides, fungicides and herbicides [80] and 5-amino-2,4'-thiobispyridine and the corresponding 2,4'-sulfonylbispyridine possess anti-tubercular activi-

ty [141,144]. Some partly reduced 2,4'-thiobispyridines have been patented as analgesics [145].

D. 3,3'-Thiobispyridine.

The most efficient method of preparing 3,3'-thiobispyridine (**27**) involves reaction of pyridine-3-thiol (**40**) with 3-bromopyridine (**17**) in the presence of cuprous oxide and

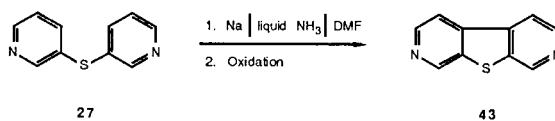


potassium carbonate in a sealed vessel at 180° whereby 3,3'-thiobispyridine is obtained in 63% yield [146]. In an earlier longer method 3-bromopyridine 1-oxide was allowed to react with potassium hydrogen sulfide in the presence of cupric ions at 140° to give 3,3'-thiobispyridine 1,1'-dioxide which was deoxygenated to 3,3'-thiobispyridine with phosphorus trichloride in chloroform [147]. 3,3'-Thiobispyridine is also obtained in low yield by reacting 3-bromopyridine with sodium sulfide in dimethyl sulfoxide at 150° [103]. A somewhat similar route has been used to prepare 4,4'-dinitro-3,3'-thiobispyridine 1,1'-dioxide from 3-fluoro-4-nitropyridine 1-oxide and thiourea or thioacetamide [148,149]. A few routes to substituted 3,3'-thiobispyridines have been described. Thus, 6,6'-dihydroxy-3,3'-thiobispyridine is formed in 13% yield from the reaction of 2-hydroxypyridine with sulfur dichloride at 200° [150] and has been converted to various phosphorus esters [151] while 6,6'-bis-(2-pyridyl)-3,3'-thiobispyridine is obtained by heating the sodium salt of 2,2'-bipyridine-5-sulfonic acid at $500\text{--}600^\circ$ [152].

In reactions of 3,3'-thiobispyridine it forms a diquaternary salt with methyl iodide. The salt is reduced polarographically by a one electron transfer not involving hydrogen to an unstable radical cation at a potential (E_0) of -0.72 V in aqueous solution [146].

3,3'-Thiobispyridine and its 1,1'-dioxide are oxidized to 3,3'-sulfonylbispyridine 1,1'-dioxide with hydrogen peroxide in trifluoroacetic anhydride. Deoxygenation of the latter to 3,3'-sulfonylbispyridine is accomplished with phosphorus trichloride. 3,3'-Sulfonylbispyridine is oxidized back to the 1,1'-dioxide with hydrogen peroxide in trifluoroacetic anhydride. On the other hand oxidation of 3,3'-thiobispyridine with hydrogen peroxide in acetic acid affords the sulfoxide [147]. 6,6'-Bis-(2-pyridyl)-3,3'-thiobispyridine gives the corresponding sulfone on oxidation with potassium dichromate [152].

Reaction of 3,3'-thiobispyridine with sulfur at $155\text{--}180^\circ$ affords a low yield of 3-methylthiopyridine after methylation of the product with dimethyl sulfate [103]. In an interesting intramolecular ring closure, 3,3'-thiobispyridine



(**27**) has been found to be converted to thieno[2,3-c:5,4-c']-dipyridine (**43**) with sodium and liquid ammonia in dimethylformamide followed by aerial oxidation [153].

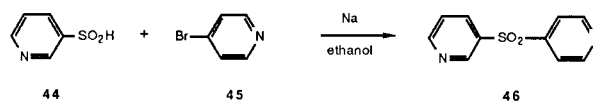
In spectral studies the mass spectrum of 3,3'-thiobispyridine has been studied. The base peak is due to the molecular ion which fragments by loss of H, HCN and CS as well as by rupture of the central bonds [146].

In possible practical applications the 1,1'-dimethyl diquaternary salt of 3,3'-thiobispyridine was found to be inactive as a herbicide [146].

E. 3,4'-Thiobispyridine.

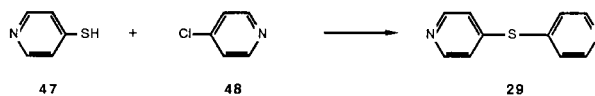
The only paper concerned with 3,4'-thiobispyridine (**28**) reports its formation in 95% yield by heating pyridine-4-thiol with pyridine-3-thiol at 140° in ligroin. It is an oil although no physical constants were recorded [78].

3,4'-Sulfonylbispyridine (**46**) has, however, been prepared by reacting pyridine-3-sulfonic acid (**44**) with 4-bromopyridine (**45**) in the presence of sodium in ethanol [154]. 3,4'-Sulfonylbispyridine gives a methbromide with methyl bromide and is claimed to have anthelmintic activity [154].



F. 4,4'-Thiobispyridine.

There are several routes for the preparation of 4,4'-thiobispyridines. The parent compound was first obtained in 1939 as a by-product of the reaction of 4-mercaptopyridine with chlorine in acetic acid where the principal product was 4-chloropyridine [155]. One of the most satisfactory routes involves reaction of 4-mercaptopyridine (**47**) with 4-chloropyridine (**48**) to afford 4,4'-thiobispyridine (**29**)



[156] and modifications of this method have been applied to the synthesis of various substituted 4,4'-thiobispyridines [141,142,157-159]. Sometimes some of the disulfide is formed as well [142] and occasionally anomalous results have been reported. Thus 4-mercaptopyridine and 4-chloro-3-nitropyridine in the presence of acetone and potassium carbonate afford the parent compound 4,4'-thiobispyridine, the nitro group apparently being removed in the

process [142] and surprisingly 4-mercapto-3-nitropyridine and 2-bromopyridine in the presence of copper powder gives 3,3'-dinitro-4,4'-thiobispyridine [142]. Another closely related route to the synthesis of 4,4'-thiobispyridines involves reaction of 4-halogenated pyridines with thiourea [159-163], potassium hydrogen sulfide [164,165], hydrogen sulfide [162], sodium thiosulfate [166] or sodium sulfide [166]. These methods have also been applied to the synthesis of 4,4'-thiobispyridine 1,1'-dioxides from 4-halogenated pyridine 1-oxides [162,167,170]. It has also been found that reaction of 2,3,5,6-tetrabromo-4-methylsulfonylpyridine with sodium hydrogen sulfide affords perbromo-4,4'-thiobispyridine, the methylsulfonyl group behaving in this case like a halogen group [171].

In another route to 4,4'-thiobispyridines, 1-(4-pyridyl)pyridinium chloride (**18**) and related salts react with pyridine-4-thiol, thiourea or hydrogen sulfide to give 4,4'-thiobispyridines [79,80,119,172] sometimes in about 90% yield. 4,4'-Thiobispyridine is also obtained by heating pyridine-4-thiol [173] especially high yields being forthcoming if decalin is used as solvent and heating is continued until evolution of hydrogen sulfide ceases [78]. It is also formed by reduction of pyridine-4-sulfonyl chloride with hydrazine in 29% yield [174].

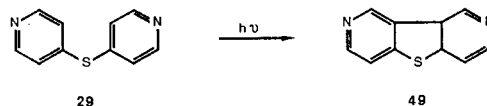
In miscellaneous routes to 4,4'-thiobispyridines, 4,4'-thiobispyridine is among the products formed from the rearrangement of pyridine-4-thione-1-carboxylates with heat and light [175] while 2,2',6,6'-tetra-*t*-butyl-4,4'-thiobispyridine is among the products obtained from the reaction of *t*-butyllithium with 2-*t*-butyl-4-methylthiopyridine [164,176]. 2,2',6,6'-Tetra-*t*-butyl-4,4'-thiobispyridine is also formed from 4-hydroxy-2,6-di-*t*-butylpyridine and phosphorus pentasulfide [164]. 4-Lithio-2,3,5,6-tetrachloropyridine reacts with sulfur dichloride to give octachloro-4,4'-thiobispyridine and with thionyl chloride to give in addition some of the corresponding sulfoxide [177]. 3-Nitro-4-thiocyanatopyridine is another starting material for the preparation of 4,4'-thiobispyridines. It reacts with alkali or hot aliphatic alcohols to give 3,3'-dinitro-4,4'-thiobispyridine [178,179]. Certain substituted pyridine-4-thiuronium salts react with methanol to give 4,4'-thiobispyridine derivatives [163]. To conclude the methods which have been used to synthesise 4,4'-thiobispyridines it has been found that partly reduced 4,4'-thiobispyridines are obtained by treating piperidine derivatives with hydrogen sulfide and hydrogen chloride in ethanol [180,181].

In reactions of 4,4'-thiobispyridines some transformations of substituents by standard procedures have been reported. Thus nitro to amino [141,142] and cyano to various derived functional groups [162] have been described. In reactions involving the sulfur bridge, 4,4'-thiobispyridine is oxidized to the sulfone, 4,4'-sulfonylbispyridine, with permanganate [156] and other similar oxidations with hy-

drogen peroxide in acetic acid [164,169] or hydrogen peroxide in trifluoroacetic anhydride [158] have been described. Similar oxidations have recently been reported by others [119]. Sometimes oxidation of the nitrogens to the 1,1'-dioxide accompanied sulfone formation [177]. Sulfoxide formation has also been observed [158].

In reactions on nitrogen, 1,1'-dioxides have been deoxygenated with phosphorus trichloride [177]. 4,4'-Thiobispyridine forms the 1,1'-dimethyl diquatery salt with excess methyl iodide [172,182]. The salt is reduced in aqueous solution by a one electron transfer to the corresponding radical cation at a potential (E_0) of -0.57 V [182].

Photolysis of 4,4'-thiobispyridine (**29**) in ethanol affords, *inter alia*, the thienodipyridine (**49**) [183] and likewise photolysis of octachloro-4,4'-thiobispyridine gives the corresponding hexachlorothienodipyridine by loss of chlorine [143]. 4,4'-Thiobispyridine on reaction with sulfur at



175-200° affords some dithiins and polymers but 4-methylthiopyridine is the main product isolated after methylation of the crude product with dimethyl sulfate [103]. Cobalt and ruthenium complexes of 4,4'-thiobispyridine have been studied [184,185].

In spectral studies the mass spectrum of 4,4'-thiobispyridine reveals that the base peak is due to the molecular ion. Fragmentation routes involve loss of H, CS, S, HCN and C_2HS as well as rupture of the central bonds [41]. Ultraviolet and ^{19}F nuclear magnetic resonance spectra of polyfluoro-4,4'-thiobispyridine and its sulfone and sulfoxide have been reported [158] while the X-ray fluorescence spectrum of perfluoro-4,4'-thiobispyridine was included in a study of the conjugation of the sulfur bridge with the rings in a series of diaryl sulfides [186].

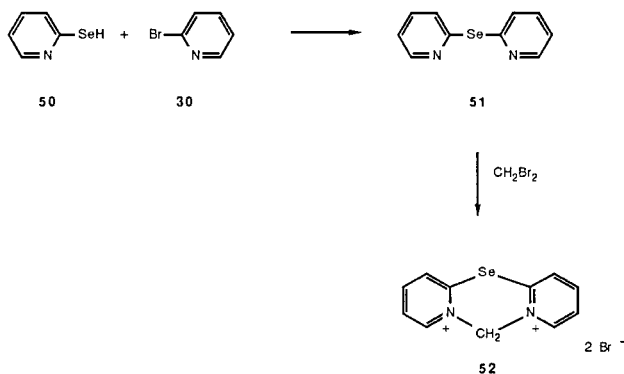
Several practical applications of 4,4'-thiobispyridines have been discovered. 4,4'-Thiobispyridines [80] and polyhalogen substituted derivatives [157] have been patented as bactericides, fungicides, herbicides, nematocides and pesticides and appear to be included in further anti-bacterial, anti-fungal and anti-tumour tests [119]. 3-Amino-4,4'-thiobispyridine [141,144] and some thioamido substituted 4,4'-thiobispyridines and their 1,1'-dioxide analogues have been shown to have pronounced anti-tubercular activity [162]. 4,4'-Thiobispyridine is effective as promoter of electron transfer to cytochrome C at a gold electrode [187-189] while some partly reduced derivatives of 4,4'-thiobispyridine are useful as antioxidants for polymers [180,181].

IV. Selenobispyridines.

Only two selenobispyridines, the 2,2'- and 4,4'-isomers have been studied.

A. 2,2'-Selenobispyridine.

2,2'-Selenobispyridine (**51**) was prepared in 1978 in 80% yield by condensation of 2-selenopyridine (**50**) with 2-bromopyridine (**30**). It is a yellow oil [190]. It has also been obtained in 20% yield as a by-product of the preparation of 2-pyridyl phenyl selenide [191].

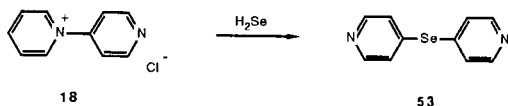


2,2'-Selenobispyridine forms the diquaternary salt 6*H*-dipyrido[2,1-*b*:1',2'-*e*]1,3,5-selenadiazium dibromide (**52**) by refluxing with dibromomethane [190].

In the mass spectrum of 2,2'-selenobispyridine the base peak is at mass 78 due to the $\text{C}_5\text{H}_4\text{N}^+$ ion formed principally by rupture of the central bonds. The molecular ion gives rise to a peak of 50% of the intensity of the base peak. Other fragmentations include loss of H, Se and CSe from the molecular ion and HCN from the M-1 ion [192].

B. 4,4'-Selenobispyridine.

4,4'-Selenobispyridine (**53**) is formed by reaction of 1-(4-pyridyl)pyridinium chloride (**18**) with hydrogen selenide in pyridine solution. 4,4'-Selenobispyridine is a low melting solid. Some of the corresponding diselenide is formed as a by-product [172]. Instead of hydrogen selenide, potassium or sodium hydrogen selenides may be used in the reaction [193,194].



4,4'-Selenobispyridines have bactericidal and herbicidal properties [193,194].

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