Synthetic Pathways of the Chalcogenobispyridines

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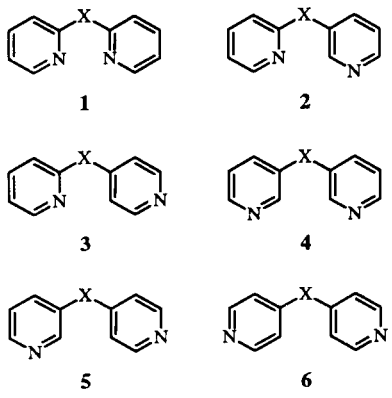
Introduction.

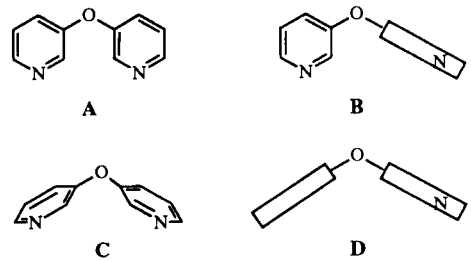
There are six chalcogenobispyridine isomers, whose structures are 2,2'-(**1**), 2,3'-(**2**), 2,4'-(**3**), 3,3'-(**4**), 3,4'-(**5**) and 4,4'-(**6**). In 1987 Summers [1] reviewed the chemistry of the chalcogenobispyridines and showed that only two complete families of six isomers (the oxy- and thiobispyridines) have been synthesized; syntheses of only the 2,2'- and 4,4'-selenobispyridines were recorded, while none of the tellurobispyridines had been generated. Recently, Summers and coworkers [2-14] have achieved the synthesis of all the isomers of the chalcogenobispyridines.



1 **2** **3** **4** **5** **6**

The wide range of biological and industrial applications displayed by the oxy- and thiobispyridines warrants a thorough and systematic review of the synthesis of these compounds. For example, 2,2'-oxybispyridine is a suitable ligand for a cobalt carbonyl complex catalyst, and so is useful in the hydroformylation of olefins [15-16]. 2,3'-Oxybispyridine is claimed to have both psychotropic and bactericidal properties [17], whereas 3,3'-oxybispyridine and its *N*-oxides have been found to influence the learning ability of mice [18]. In case of the thiobispyridines, the 2,2'- isomer shows pronounced activity against streptococcus infections of rabbits [19] and also some anti-thyroid [20-21], anti-bacterial, anti-fungal and anti-tumor activity [22]. 2,4'-Thiobispyridines have been patented as bactericides, fungicides and herbicides [23], with substituted 4,4'-thiobispyridines [23] being patented as bactericides, fungicides, herbicides, nematocides and pesticides. 4,4'-Thiobispyridine is itself an effective promoter of electron transfer to cytochrome C at a gold electrode [24-26] and has been patented as an additive in photosensitive layers for electrophotography [27]. The biological activity of seleno- and tellurobispyridines have not yet been explored.

Conformational analysis of the chalcogenobispyridines is an important precursor to understanding their biological activity [28-29]. The four postulated structures of the chalcogenobispyridines (for the case of 3,3'-oxybispyridines) are shown in Figure 1: **A** planar structure; **B** the "Morino" structure which is based upon electron diffraction [30], dielectric relaxation [31] and infrared spectroscopy [32-33] studies; **C** a structure in which both rings are rotated at various angles relative to the C-O-C plane, which is based upon investigations of molar Kerr constants [34-35], optical anisotropy [36], dielectric relaxation [37], uv spectroscopy [38] and vibrational spectroscopy [39]; **D** the "butterfly" structure with both phenyl rings orthogonal to the C-O-C plane. The conformational properties of the chalcogenobispyridines, calculated by Dunne, Summers and von Nagy-Felsobuki [9-10,13-14,39-40] using ab initio methods, show that the preferred confirmation of these congeners vary only slightly down the group. As anticipated, there is a contraction of the inter-ring angle and an elongation of R_{C-X} bond lengths for congeners down the group. In all cases, the minimum energy structures are predicted by the STO-3G(*)//STO-3G(*) models to be of the 'propeller' (C) or 'Morino' (**B**) forms with an almost perpendicular attitude being maintained between the ring planes. Hence, while some of the isomers of chalcogenobispyridines closely mimic the conformational behavior of diphenyl ether, the presence of ortho ring-nitrogens in isomers containing a 2-pyridyl group results in structural relaxation, due to the removal of neighboring *ortho*-hydrogen interactions.



A **B** **C** **D**

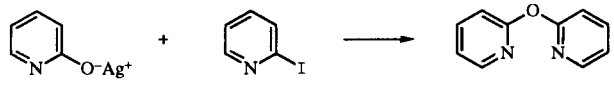
Figure 1. **A-D** Conformers for 3,3'-Oxybispyridine.

As an extension of our work [1-14,39-40] we are now able to report a thorough and systematic study of synthetic pathways to all the isomers of chalcogenobispyridines. The lack of data in this area, makes this review of the synthesis of these twenty-four compounds timely, especially since little experimental work has been

documented on the metal ligand properties of the more electron-dense members of this family.

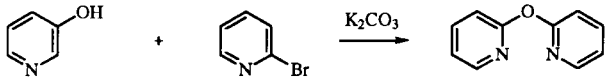
II. Oxybispyridines.

The first preparation of 2,2'-oxybispyridine (**9**) was recorded in 1957 by de Villiers and den Hertog [41] and involved heating the silver salt of 2-hydroxypyridine (**7**) together with 2-iodopyridine (**8**) to give 2,2'-oxybispyridine (**9**) in moderate yield [3,41]. The di-*p*-toluenesulfonate salt of 2,2'-oxybispyridine had been reported earlier as a by-product of the reaction of picolinic acid 1-oxide with *p*-toluenesulfonyl chloride [42]. A number of substituted 2,2'-oxybispyridines have been prepared by reaction of activated 2-halopyridines with substituted 2-hydroxypyridines using modifications of this procedure [43-45]. The dehydration of 2-hydroxypyridine in benzene solution at 170° under pressure also leads to the generation of 2,2'-oxybispyridine [46-47].



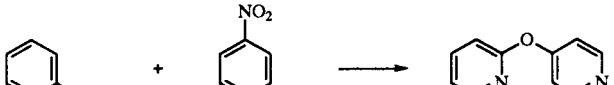
7 **8** **9**

The parent and some substituted 2,3'-oxybispyridines have been prepared by reaction of 3-hydroxypyridines (*eg* **10**) with 2-halopyridines (*eg* **11**) [41,45,48-50]. The reaction of pyridine 1-oxide with 2-pyridyl *p*-toluenesulfonate [51], 2-pyridyl *p*-toluenesulfonyl chloride [41] or 2-bromopyridine [52-53] also lead to the generation of 2,3'-oxybispyridine (**12**). 2-Pyridyl *p*-toluenesulfonate undergoes a thermal reaction to give a low yield of 2,3'-oxybispyridine [41]. Derivatives of 2,3'-oxybispyridine have been detected upon pyrolysis of 1-(5-nitro-2-pyridyl)-3-hydroxypyridinium chloride [54] and photolysis of 1-(5-nitro-2-pyridyloxy)-4,6-diphenyl-2-pyridone [55].



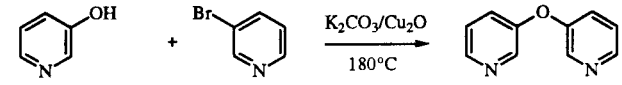
10 **11** **12**

2,4'-Oxybispyridine (**15**) has been obtained Rockley and Summers [6] by heating 4-nitropyridine (**14**) between 200° and 250° with the silver salt of 2-hydroxypyridine (**13**). A substantial amount of 1-(4-pyridyl)-4-pyridone was generated as a by-product. The reaction of a 2-halopyridine with 4-hydroxypyridines in the presence of base [45] has led to the synthesis of a number of substituted 2,4'-oxybispyridines.



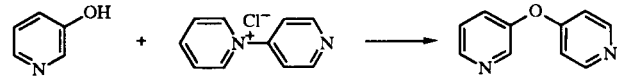
13 **14** **15**

Barker and Summers [7] reacted 3-bromopyridine (**17**) with 3-hydroxypyridine (**16**) in a sealed tube at 180° in the presence of potassium carbonate and cuprous oxide leads to the generation of 3,3'-oxybispyridine (**18**). In a more complicated process, 3-bromopyridine 1-oxide was 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 (**18**) [56]. Similarly, 3-fluoro-4-nitropyridine 1-oxide was reacted with 3-hydroxypyridine to give 4-nitro-3,3'-oxybispyridine 1-oxide, which was converted to 3,3'-oxybispyridine by reduction of the *N*-oxide and nitro functionalities, followed by deamination procedures [57].



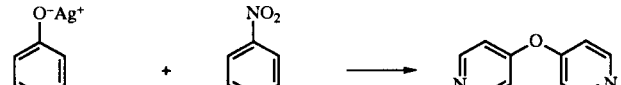
16 **17** **18**

3,4'-Oxybispyridine (**20**) has been synthesized by heating 1-(4-pyridyl)pyridinium chloride (**19**) with 3-hydroxypyridine (**16**) [58].



16 **19** **20**

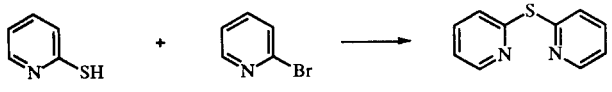
The first authentic synthesis of 4,4'-oxybispyridine (**22**) was reported in 1976 when it was formed in low yield (4%) by the reaction of pyridine 1-oxide with trichloroacetyl chloride [59]. 4,4'-Oxybispyridine is also formed in low yield by reaction of 1-(4-pyridyl)pyridinium chloride (**19**) with 4-hydroxypyridine [58]. Heating the silver salt of 4-hydroxypyridine (**22**) with 4-nitropyridine (**14**) also leads to the formation of 4,4'-oxybispyridine, although still in moderate yield [5]. 3,3',5,5'-Tetranitro-4,4'-oxybispyridine has been prepared by dehydration of 3,5-dinitro-4-hydroxypyridine with *p*-toluenesulfonyl chloride in the presence of *N,N*-diethylaniline [60].



21 **14** **22**

III. Thiobispyridines.

The first synthesis of 2,2'-thiobispyridine (**24**) was recorded in 1937 and involved the reaction of 2-bromopyridine (**11**) with cupric thiocyanate in methanol [61]. A more widely used method of preparing the parent and substituted 2,2'-thiobispyridines involves reacting 2-halopyridines with 2-mercaptopyridines (**23**) in hot benzene [62-64].



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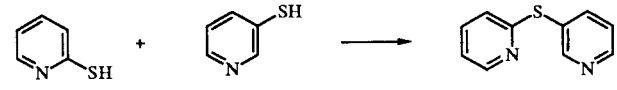
The reaction of 2-halopyridines with sodium sulfide or other alkali metal sulfides also leads to the formation of 2,2'-thiobispyridines [65-69]. Yields in this process have been improved by use of phase transfer catalysts [70]. Potassium hydrogen sulfide [71-72], thiourea [43,73-75], thioacetamide [75], diethyl phosphothioates [76] and 2-mercaptobenzimidazole [77] can all be substituted for sodium sulfide. Heating 2-mercaptopyridine alone at 240° gives 2,2'-thiobispyridine in 80% yield [78], while heating 1-(2-pyridyl)pyridinium iodide with 2-mercaptopyridine [79-80] also leads to its formation in more moderate yield.

The formation of 2,3'-thiobispyridine (**26**) in 90% yield was achieved by heating 2-mercaptopyridine (**23**) with 3-mercaptopyridine (**25**) at 160° in ligroin [78]. Reaction of 2-amino-5-iodopyridine with 2-mercaptopyridine in the presence of sodium methoxide gave 6'-amino-2,3'-thiobispyridine [81] and similarly, condensation of 3-mercaptopyridine with 2-chloro-3-nitropyridine gave 3-nitro-2,3'-thiobispyridine [82].



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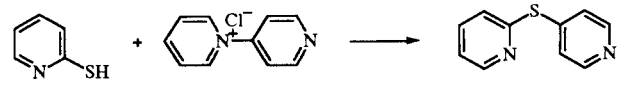
Heating 1-(4-pyridyl)pyridinium chloride (**19**) with 2-mercaptopyridine (**23**) afforded 2,4'-thiobispyridine (**27**) in good yield [79-80]. 2- and 4-Mercaptopyridine reacted with activated 4- and 2-halopyridines giving a number of substituted 2,4'-thiobispyridines [82-83]. In an interesting reaction, 3-nitro-4-chloropyridine reacted with the sodium salt of 2-mercapto-3-hydroxypyridine to give 3-hydroxy-3'-nitro-2,4'-thiobispyridine which immediately ring-closed to a dipyridooxathiin [50].



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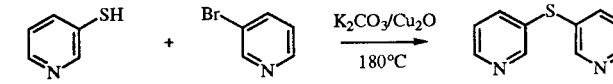
The reaction of 3-mercaptopyridine (**25**) with 3-bromopyridine (**17**) in the presence of cuprous oxide and potassium carbonate in a sealed vessel at 180° affords 3,3'-thiobispyridine (**28**) in 63% yield [8]. The reaction of 3-bromopyridine 1-oxide with potassium hydrogen sulfide in the presence of cupric ions at 140° to gave 3,3'-thiobispyridine 1,1'-dioxide. Deoxygenation with phosphorous trichloride in chloroform gave 3,3'-thiobispyridine [84]. The reaction of 3-bromopyridine (**17**) with sodium sulfide in dimethyl sulfoxide at 150° also leads to the formation of 3,3'-thiobispyridine in low yield [85]. Related methods utilize thiourea and thioacetamide in place of sodium sulfide [86-87]. 6,6'-Dihydroxy-3,3'-thiobispyridine is formed in 13% yield from the reaction of 2-hydroxypyridine with sulfur dichloride at 200° [88] and 6,6'-bis-(2-pyridyl)-3,3'-thiobispyridine is obtained by heating the sodium salt of 2,2'-bipyridine-5-sulfonic acid at 500-600° [2].



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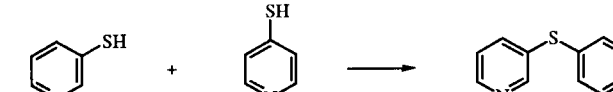
3,4'-Thiobispyridine (**30**) has been formed in 95% yield by heating 4-mercaptopyridine (**29**) with 3-mercaptopyridine (**25**) at 140° in ligroin [78].



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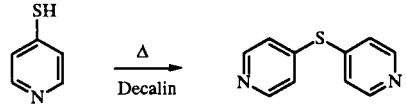
4,4'-Thiobispyridine (**31**) was first obtained in 1939 as a by-product of the reaction of 4-mercaptopyridine (**29**) with chlorine in acetic acid [89]. The reaction of 4-mercaptopyridine (**29**) with 4-chloropyridine affords 4,4'-thiobispyridine in good yield and modifications of this procedure have been used for the synthesis of a number of substituted 4,4'-thiobispyridines [83,90-93]. 4-Mercapto-3-nitropyridine and 2-bromopyridine in the presence of copper powder surprisingly gives 3,3'-dinitro-4,4'-thiobispyridine [90]. Reactions of 4-halogenated pyridines and 4-halogenated pyridine 1-oxides with thiourea, potassium hydrogen sulfide, hydrogen sulfide, sodium thiosulfate or sodium sulfide also lead to the synthesis of 4,4'-thiobispyridines and 4,4'-thiobispyridine 1,1'-oxides respectively [93-102]. The reaction of 2,3,5,6-tetrabromo-4-methylsulfonylpyridine with sodium hydrogen sulfide affords perbromo-4,4'-thiobispyridine [103].

1-(4-Pyridyl)pyridinium chloride and related salts react with 4-mercaptopyridine, thiourea or hydrogen sulfide to give 4,4'-thiobispyridines [79-80,104-105], sometimes in 90% yield. 4,4'-Thiobispyridine (**31**) is also obtained by heating 4-mercaptopyridine (**29**) in high boiling solvents like decalin until evolution of hydrogen sulfide ceases [106]. The reduction of pyridine-4-sulfonyl chloride with hydrazine [107] and the rearrangement of pyridine-4-thione-1-carboxylates with heat and light [108] leads to the formation of 4,4'-thiobispyridine in moderate yield. The reaction of *t*-butyllithium with 2-*t*-butyl-4-methylthiopyridine [98,109] and 4-hydroxy-2,6-di-*t*-butylpyridine with phosphorus pentasulfide [98] produces some 2,2',6,6'-tetra-*t*-butyl-4,4'-thiobispyridine. 4-Lithio-2,3,5,6-tetrachloropyridine reacts with sulfur dichloride to give octachloro-4,4'-thiobispyridine, while its reaction

with thionyl chloride leads to the generation of both the thiobispyridine and its corresponding sulfoxide [110]. 3-Nitro-4-thiocyanatopyridine reacts with alkali or hot aliphatic alcohols to give 3,3'-dinitro-4,4'-thiobispyridine [111-112].



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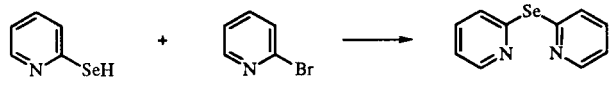
IV. Selenobispyridines.

Prior to 1992, only two of the selenobispyridines - the 2,2'- and 4,4'-isomers were characterized. In 1978, Grant and Summers [4] prepared 2,2'-selenobispyridine (**32**) in 80% yield by condensation of pyridine-2-selenol (**33**) with 2-bromopyridine (**11**). In a later synthesis, 2,2'-selenobispyridine was formed in 65% yield by treating the 2-pyridylselenolate anion (generated from the sodium reduction of 2-methylselenylpyridine) with 2-bromopyridine in hexamethylphosphoramide (HMPA) at 120° [113]. 2,2'-Selenobispyridine has also been reported as a by-product in the generation of bis-(2-pyridyl) diselenide from lithium diselenide and 2-bromopyridine in tetrahydrofuran (THF) and HMPA [114] and in the preparation of 2-pyridyl phenyl selenide [115].



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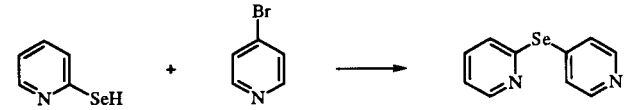
In 1992 Dunne *et al.* [11] obtained 2,2'-selenobispyridine (**32**) in 88% yield by the reaction of 2-bromopyridine (**11**) with pyridine-2-selenol (**33**) in 2-ethoxyethanol. The pyridine-2-selenol was generated *in situ* from 2-bromopyridine and sodium hydrogen selenide, the latter being obtained from the reduction of selenium powder with sodium borohydride in 2-ethoxyethanol by adaptation of the method reported by Klayman and Griffin [116]. This procedure represents an improvement over the earlier method [4], since the isolation of the pyridine-2-selenol is not required. While sodium hydrogen selenide could be generated quite readily in ethanol [116], its reaction with 2-bromopyridine was found not to proceed in this solvent, necessitating the use of 2-ethoxyethanol. Compared with the reduction of elemental selenium with sodium borohydride in ethanol, the corresponding reaction in 2-ethoxyethanol was very exothermic, requiring careful addition of solvent to the dry-mixed reactants.

Similarly, Dunne *et al.* [11] obtained 2,4'-selenobispyridine (**34**) in 80% yield by reaction of 4-bromopyridine (**35**) with pyridine-2-selenol (**36**) in 2-ethoxyethanol. It was found to be a yellow oil.



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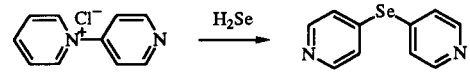
4,4'-Selenobispyridine (**36**) has been generated by reaction of 1-(4-pyridyl)pyridinium chloride (**13**) with hydrogen selenide in pyridine solution. Some of the corresponding diselenide is formed as a by-product [105]. Instead of hydrogen selenide, potassium or sodium hydrogen selenides have been used to produce 4,4'-selenobispyridine and its polyalkylated derivatives [117-118].



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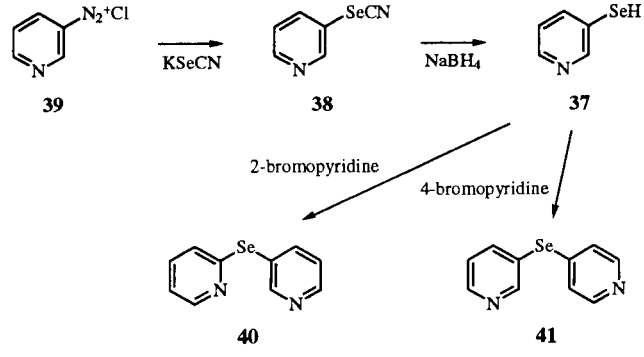
Dunne *et al.* [11] found that the preparation of the remaining isomers required the generation of the previously unknown pyridine-3-selenol (**37**) (although the corresponding anion has been reported [113]). In a similar method to the synthesis of pyridine-3-thiol, pyridine-3-selenol was generated from the reduction of the corresponding chalcogenocyanate. The preparation of the new 3-selenocyanatopyridine (**38**) was achieved by diazotization of 3-aminopyridine followed by reaction of the pyridine-3-diazonium salt (**39**) with potassium selenocyanate [11]. The 3-selenocyanatopyridine was reduced to pyridine-3-selenol with sodium borohydride in 2-ethoxyethanol. Without isolation, the pyridine-3-selenol was then reacted with either 2- or 4-bromopyridine to give 2,3'- or 3,4'-selenobispyridine (**40**,**41**) respectively, both in good yield.



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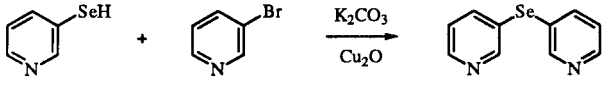
Dunne *et al.* [11] obtained the 3,3'-selenobispyridine (**42**) from 3-bromopyridine (**17**) and pyridine-3-selenol (**37**) by heating them together at 180° in a sealed tube in the presence of potassium carbonate and cuprous oxide in an analogous method to the reported syntheses of 3,3-oxybispyridine [7] and 3,3'-thiobispyridine [8]. This synthesis required the isolation of pyridine-3-selenol, which

was achieved by adjusting the *p*H of the solution to ~5.5 (after reduction of 3-selenocyanatopyridine) with a concentrated sodium hydroxide solution, followed by an extraction with chloroform. The product was obtained as a dark yellow oil with a disagreeable odor in 75% yield.



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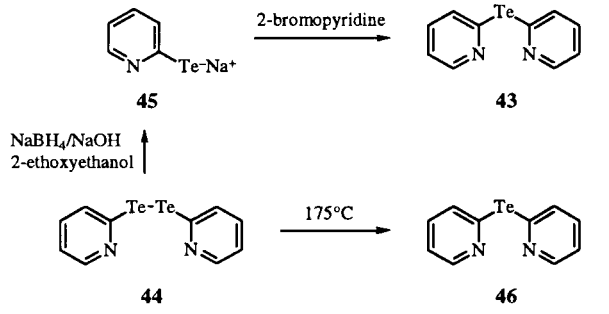
V. Tellurobispyridines.

Dunne *et al.* [12] prepared 2,2'-tellurobispyridine (**43**) by two methods. The first involved the sodium borohydride reduction of 2,2'-dipyridyl ditelluride (**44**) [13] in 2-ethoxyethanol to form sodium 2-pyridyltellurolate (**45**), which was refluxed with 2-bromopyridine to afford 2,2'-tellurobispyridine in 83% yield.



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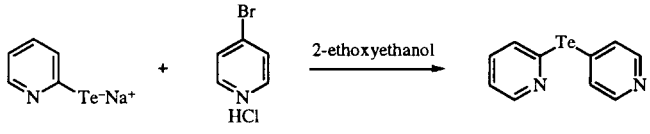
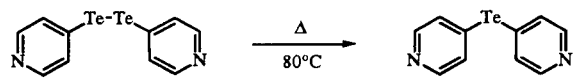
The second method involved the thermal detellurization of 2,2'-dipyridyl ditelluride (**46**). The ditelluride was heated to 175° for 1 hour to obtain the monotelluride in 68% yield. Increased reaction times and temperatures resulted in the decomposition of the product to elemental tellurium and tars [12].

2,4'-Tellurobispyridine (**47**) was prepared by the reaction of sodium 2-pyridyltellurolate (**45**) with 4-bromopyridine hydrochloride (**48**) in 2-ethoxyethanol in 69% yield [12]. This reaction was found not to proceed in ethanol nor did the analogous reaction of sodium 4-pyridyltellurolate with 2-bromopyridine occur in ethanol. The latter reaction was, however, also performed in 2-ethoxyethanol resulting in a low yield of 2,4'-tellurobispyridine.



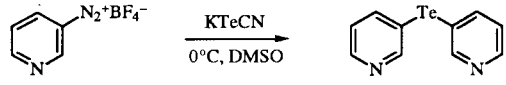
45 48 47

Dunne *et al.* [12] prepared 4,4'-tellurobispyridine (**49**) as a 13% by-product in the synthesis of 4,4'-dipyridyl ditelluride [13]. Thermal detellurization of 4,4'-dipyridyl ditelluride (**50**) was initiated at 80° and gave the monotelluride in 94% yield.



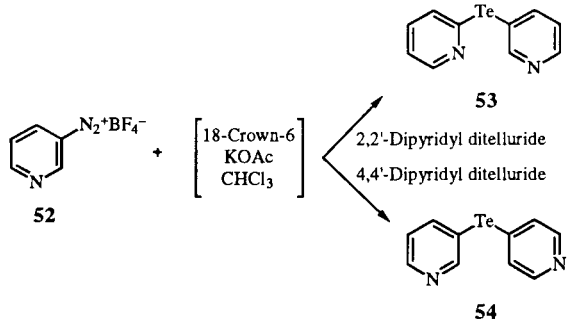
50 49

Dunne *et al.* [12] used an adaptation of the method of Engman [11] for the generation of 3,3'-tellurobispyridine (**51**). 3-Aminopyridine undergoes diazotization reactions in fluoroboric acid leading to the formation of 3-pyridyl diazonium tetrafluoroborate (**52**). This salt was then added to a chilled solution of potassium tellurocyanate in DMSO under nitrogen. Stirring at ambient temperature for 2 hours led to the formation of 3,3'-tellurobispyridine in 38% yield, which is comparable to the yields reported by Engman [11] for related compounds [12]. Only a trace of 3,3'-dipyridyl ditelluride was detected in this reaction (due to its red coloration) and was easily separated from the monotelluride by chromatography [12].



52 51

2,3'-Tellurobispyridine (**53**) and 3,4'-tellurobispyridine (**54**) were prepared by Dunne *et al.* [12] using an adaptation of the method by Luxen and Christiaens [17]. The reaction of 3-pyridyl diazonium tetrafluoroborate with 2,2'-dipyridyl ditelluride and 4,4'-dipyridyl ditelluride respectively in chloroform in the presence of potassium acetate and a catalytic amount of the phase-transfer agent, 18-crown-6, led to the formation of 2,3'- and 3,4'-tellurobispyridine in 58 and 68% yields respectively. The crown ether increases the nucleophilicity of the acetate ion, which attacks the tetrafluoroborate salt to initiate a chain of reactions leading to the formation of a 3-pyridyl radical. This radical attacks the weak Te-Te bond of the ditelluride to form the respective unsymmetrical monotellurides. The reactions were performed at 0° and under nitrogen. To the author's knowledge, these are the first examples in which diaryl ditellurides have been used in this reaction.



52 53 54

VI. Conclusion.

A comprehensive study of the synthetic routes to all isomers of the chalcogenobispyridines has been presented. New facile routes to previously reported compounds have been summarized. The physical and biological properties of the recently synthesized seleno- and tellurobispyridines warrant further study based upon the large number of applications of their lighter congeners.

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