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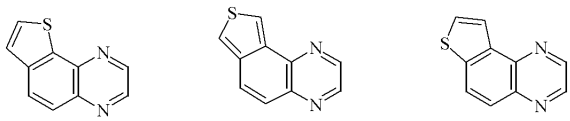
1. Introduction

The "history of thienoquinoxalines" actually began in 1950 with the synthesis of 1,3-dihydro-1,3-diphenyl-thieno[3,4-*b*]quinoxaline-2,2-dioxide by Overberger *et al.* [1]. The fusion of quinoxalines with the thiophene ring was expected to yield seven isomers of thienoquinoxalines, such as thieno[2,3-*b*] **1a**, thieno[3,4-*b*] **1b**, thieno[2,3-*f*] **2a**, thieno[3,4-*f*] **2b**, thieno[3,2-*f*] **2c**, thieno[2,3-*g*] **3a** and thieno[3,4-*g*]quinoxalines **3b** (Scheme 1).

Scheme 1

1a **1b**



2a **2b** **2c**

3a **3b**

The literature survey revealed that only three isomers of thienoquinoxalines **1a**, **1b**, and **3a** are known.

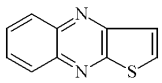
This review is concerned with the syntheses and reactions of these isomeric thienoquinoxalines during the last two decades, 1980-2000.

2. Variety of the Isomeric Thienoquinoxalines and Related Compounds.

According to the literature, the thienoquinoxalines **1a**, **1b**, and **3a** and their related compounds have received great attention. Most of these thienoquinoxalines have been prepared from the appropriate quinoxalines, and only few numbers are obtained from 2,3-difunctionalized thiophenes or benzothiophenes.

Thieno[2,3-*b*]quinoxaline (**1a**) and its derivatives are utilized as key intermediates in the synthesis of highly condensed heterocycles rather than other thienoquinoxalines (Scheme 2).

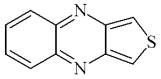
Scheme 2



1a

Roland and Anderson [2] reported the generation and attempted isolation of thieno[3,4-*b*]quinoxaline (**1b**) (Scheme 3).

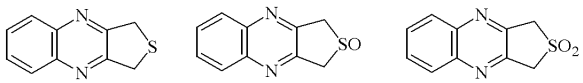
Scheme 3



1b

Dihydrogenated derivative of **1b**, 1,3-dihydrothieno-[3,4-*b*]quinoxaline **1c**, 1,3-dihydrothieno[3,4-*b*]quinoxaline-2-oxide **4**, and 1,3-dihydrothieno[3,4-*b*]quinoxaline-2,2-dioxide **5** have been also reported [2-4]. (Scheme 4)

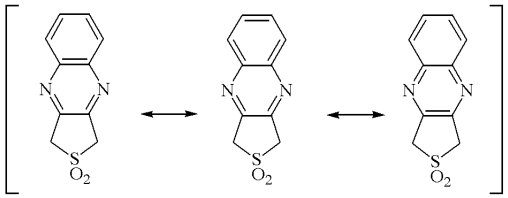
Scheme 4



1c **4** **5**

The structure of 1,3-dihydrothieno[3,4-*b*]quinoxaline-2,2-dioxide (**5**) has a special feature, and the real structure of **5** may be represented by the hybrid of the forms **5a**, **5b**, and **5c**. Forms **5a** and **5b** should make a greater contribution to the real structure due to the acquired aromatic stability [3] (Scheme 5).

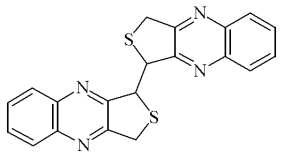
Scheme 5



5a **5b** **5c**

Dimerization of 1,3-dihydrothieno[3,4-*b*]quinoxaline (**1c**) gave 1,1'-bis(1,3-dihydrothieno[3,4-*b*]quinoxaline) (**6**) [4] (Scheme 6).

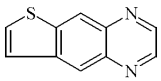
Scheme 6



6

Synthesis of the title compound **3a** was accomplished through condensation of benzothiophene derivative [5] (Scheme 7).

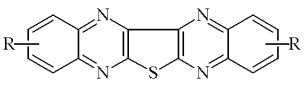
Scheme 7



3a

The skeletal structure of thieno[2,3-*b*:4,5-*b'*]diquinoxalines **7** was synthesized by photochemical reaction of cyclic dithiocarbonate [31] (Scheme 8).

Scheme 8

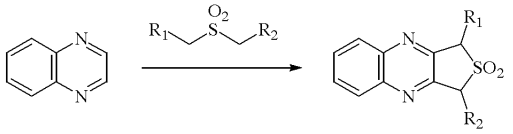


7a; R=H
7b; R=Me

3. Different Methods for the Synthesis of Thienoquinoxalines.

Thieno[3,4-*b*]quinoxaline-2,2-dioxides such as **9a-c** were prepared by the nucleophilic addition of carbanions generated from sulfones, sulfoxides, sulfides on quinoxaline (**8**) [6] (Scheme 9).

Scheme 9

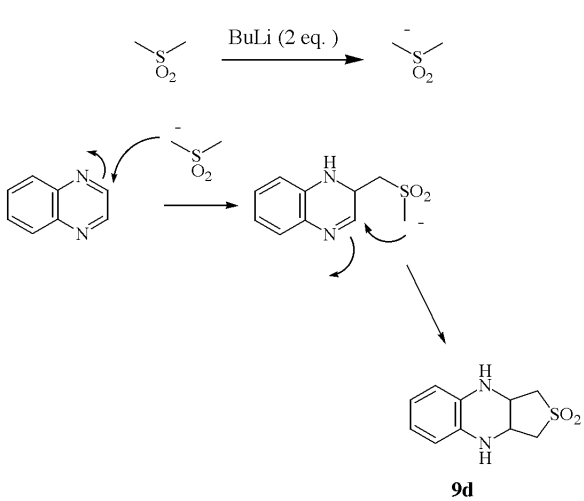


8 **9**

a; R_1=Ph, R_2=Ph
b; R_1=Me, R_2=Ph
c; R_1=SMe, R_2=H

In the same manner, dimethyl sulfone (1 mole) was metalated by butyllithium or lithium diethylamide (LDA) (1 mole) and the carbanion was allowed to react with quinoxaline (**8**) to give the adduct, 1,3,3a,4,9,9a-hexahydrothieno[3,4-*b*]quinoxaline-2,2-dioxide (**9d**) [6,7] (Scheme 10).

Scheme 10

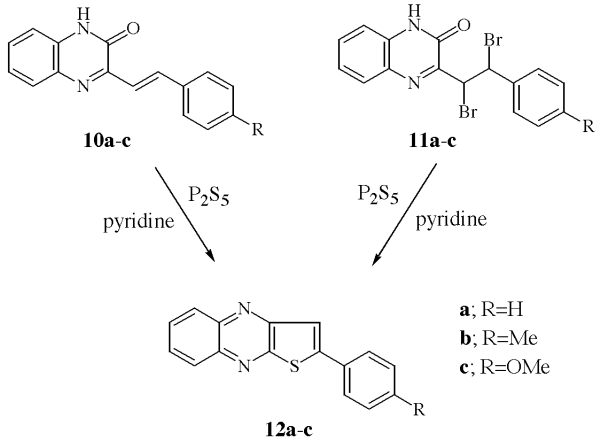


9d

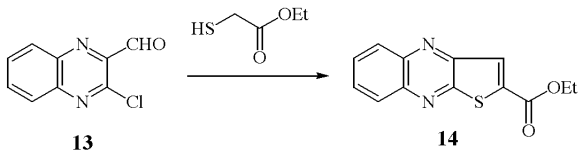
The recent reported one step conversion of 3-(substituted styryl)-2(1*H*)-quinoxalinones **10a-c** and their dibromo derivatives **11a-c** into 2-substituted thieno[2,3-*b*]-quinoxalines **12a-c** was achieved with phosphorus pentasulphide in pyridine *via* thiation, cyclization, and aromatization [8,9] (Scheme 11).

Also, 2,3-disubstituted quinoxaline **13** was reacted with ethyl thioglycolate to yield substituted thieno[2,3-*b*]-quinoxaline **14** [10,11] (Scheme 12).

Scheme 11

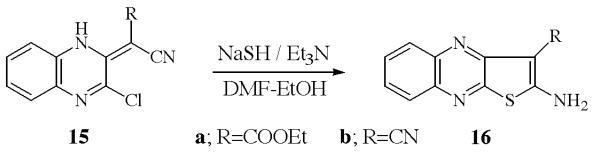


Scheme 12



Treatment of quinoxaline derivatives **15** with sodium hydrosulfide in dimethylformamide-ethanol containing triethylamine gave 3-substituted 2-aminothieno[2,3-*b*]-quinoxalines, **16a** (99%) and **16b** (88%), respectively [12] (Scheme 13).

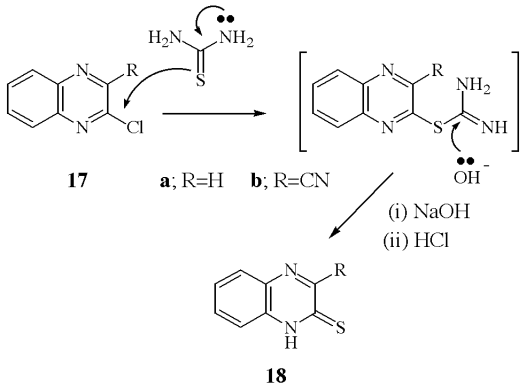
Scheme 13



Basic hydrolysis of the isothiournium salts, obtained from the reaction of 3-chloroquinoxalines **17a**, **b** with thiourea, afforded quinoxaline-2(1*H*)-thiones **18a**, **b** [13,14] (Scheme 14).

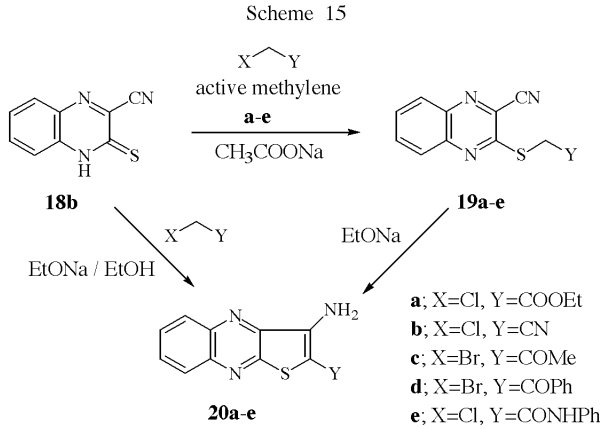
Some 2,3-disubstituted quinoxalines were used as precursors in the synthesis of different substituted thieno[2,3-*b*]quinoxalines. Thus, quinoxaline-3(4*H*)-thione-2-carbonitrile **18b** was reacted with active halomethylenes, XCH_2Y **a-e**, in the presence of sodium acetate to give **19a-e** which were cyclized with sodium ethoxide to afford the corresponding 2-functionalized 3-aminothieno[2,3-*b*]quinoxalines **20a-e** [15,16]. Thienoquinoxalines **20a-e** were also obtained directly

Scheme 14



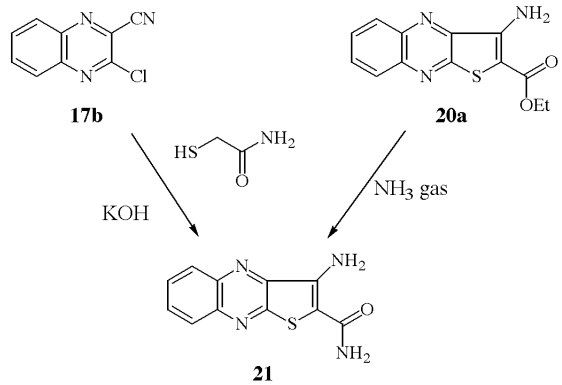
by the reaction of **18b** with the respective halocompounds in ethanol containing sodium ethoxide [14] (Scheme 15).

Scheme 15



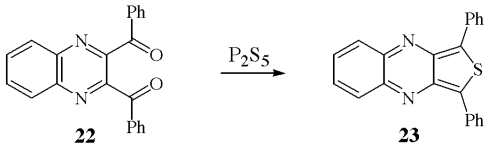
Moreover, 3-aminothieno[2,3-*b*]quinoxaline-2-carboxamide (**21**) was prepared either by the reaction of **20a** with ammonia gas or by the interaction of 3-chloroquinoxaline-2-carbonitrile **17b** with mercaptoacetamide in the presence of potassium hydroxide [17] (Scheme 16).

Scheme 16



Cyclization of 2,3-dibenzoylquinoxaline **22** with phosphorus pentasulfide yields 1,3-diphenylthieno[3,4-*b*]-quinoxaline **23** [18] (Scheme 17).

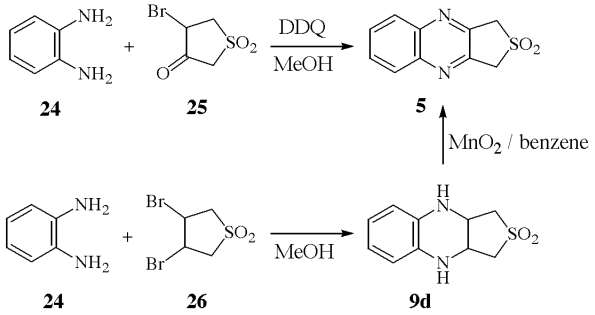
Scheme 17



The reaction of 4-bromo-3-sulfolanone **25** with *o*-phenylenediamine **24** in the presence of dichlorodicyanobenzoquinone (DDQ), yielded 1,3-dihydrothieno[3,4-*b*]quinoxaline-2,2-dioxide **5**.

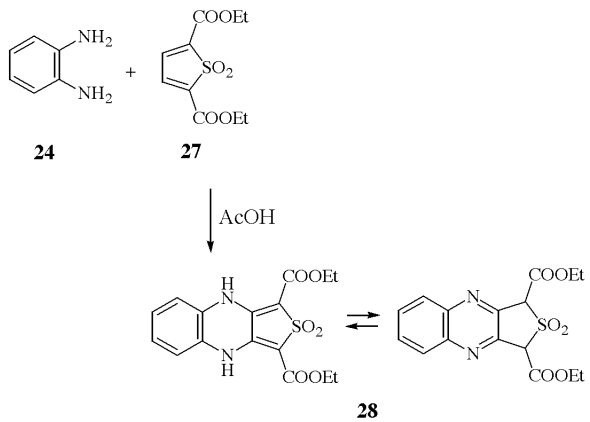
Compound **5** was also prepared from the reaction of 3,4-dibromosulfolane **26** with *o*-phenylenediamine **24**, followed by the dehydrogenation of tetrahydroquinoxaline intermediate **9d** [19,20] (Scheme 18).

Scheme 18



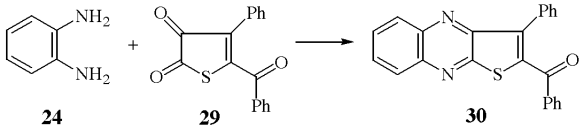
Diethyl dihydrothieno[3,4-*b*]quinoxaline-1,3-dicarboxylate **28** was obtained in 15% yield by the reaction between diester **27** and *o*-phenylenediamine **24** in acetic acid [21] (Scheme 19).

Scheme 19



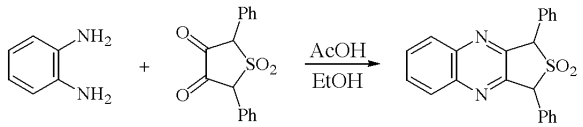
Moreover, 2-benzoyl-3-phenylthieno[2,3-*b*]quinoxaline **30** was prepared *via* the condensation of thiophene-2,3-dione derivative **29** with *o*-phenylenediamine **24** [22-24] (Scheme 20).

Scheme 20



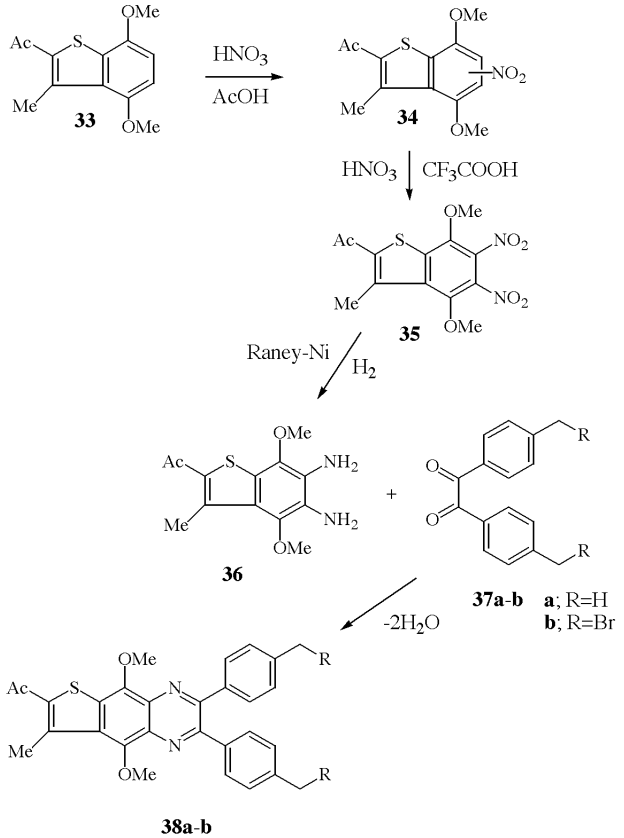
Similarly, condensation of *o*-phenylenediamine (**24**) with cyclic diketosulfone derivative **31** yielded thieno-[3,4-*b*]quinoxaline derivative **32** [25] (Scheme 21).

Scheme 21



Thieno[2,3-*g*]quinoxalines **38** were prepared by the condensation of 5,6-diaminobenzothiophene derivative **36** [26] with 4,4'-dimethylbenzil or 4,4'-dibromomethylbenzil **37** [27] (Scheme 22). The starting diamine **36** was

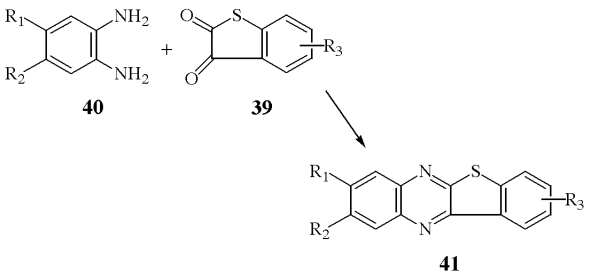
Scheme 22



obtained by the two nitration steps illustrated in Scheme 22, followed by the reduction of dinitrobenzothiophene **35**.

Condensation of benzothiophene-2,3-diones **39** with monosubstituted and disubstituted *o*-phenylenediamines **40** have been reported to give the corresponding benzothieno[2,3-*b*]quinoxalines **41** [28] (Scheme 23).

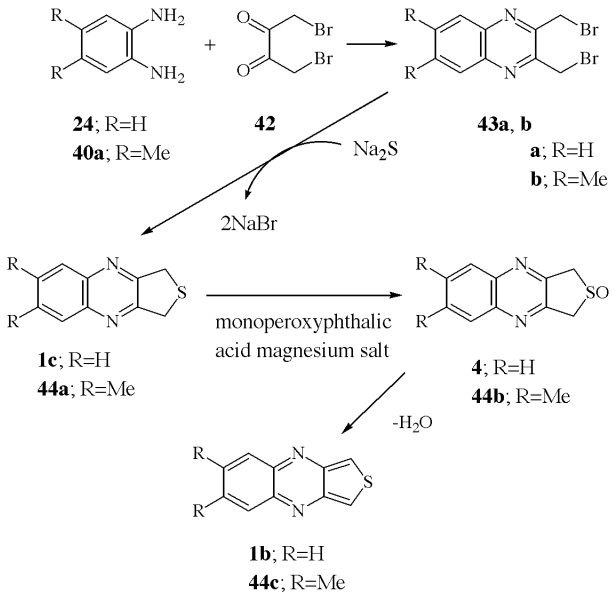
Scheme 23



R_1, R_2 = H, Me, OMe, NO_2, halo
R_3 = H, Me, Br

It has been found that the reaction of 1,4-dibromo-2,3-butanedione **42** with *o*-phenylenediamine **24** and its 4,5-dimethyl derivative **40a** gave 2,3-di(bromomethyl)-

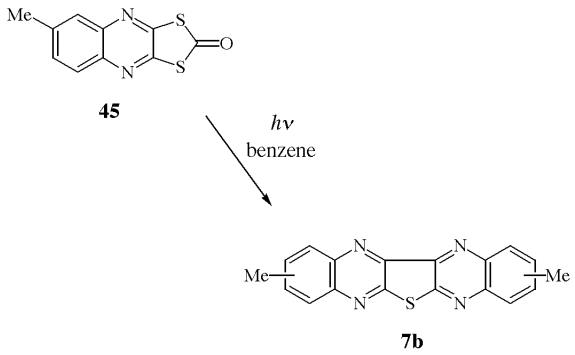
Scheme 24



quinoxalines **43a**,**b**, respectively. Compounds **43a**,**b** were converted into the corresponding dihydrothienoquinoxalines **1c** and **44a** by treatment with anhydrous sodium sulfide, followed by oxidation and dehyration to give thieno[3,4-*b*]quinoxalines **1b** and **44c**, respectively [4,29] (Scheme 24).

The irradiation to 6-methylquinoxaline cyclic dithiocarbonate **45** [30] at 280 nm in benzene, led to the formation of dimethylthineo[2,3-*b*:4,5-*b'*]diquinoxaline **7b** [31] (Scheme 25).

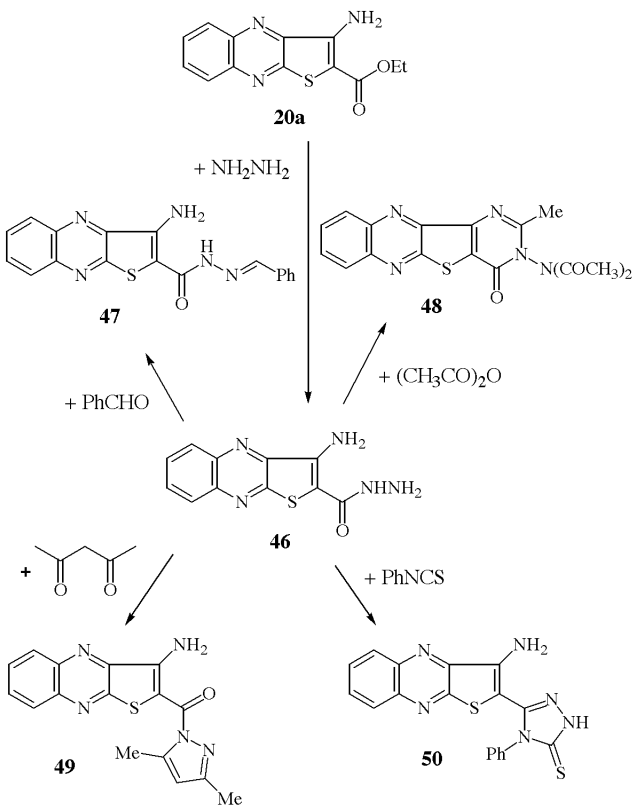
Scheme 25



4. Reactions of the Thienoquinoxalines.

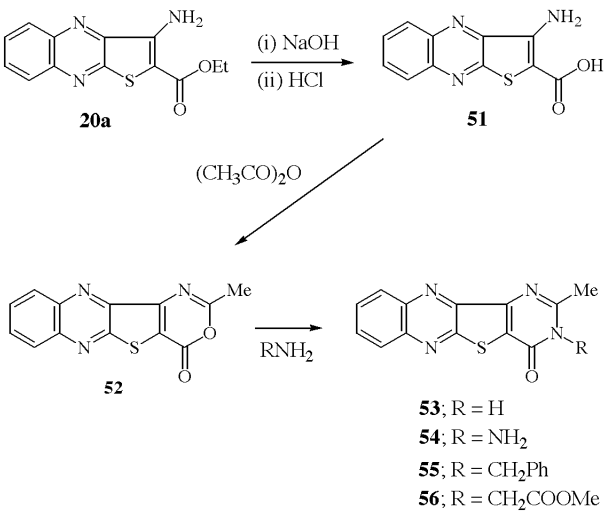
Hydrazinolysis of ethyl 3-aminothieno[2,3-*b*]quinoxaline-2-carboxylate (**20a**) yielded the corresponding 2-carbohydrazide **46** which was reacted with aromatic aldehyde, acetic anhydride, acetylacetone and phenyl isothiocyanate to give the corresponding thieno[2,3-*b*]-quinoxalines **47-50**, respectively [15,32] (Scheme 26).

Scheme 26



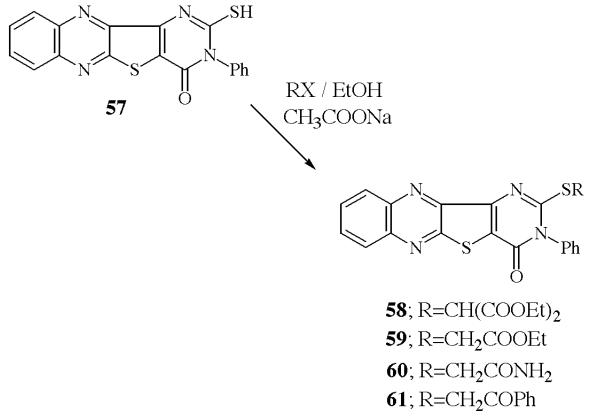
Moreover, hydrolysis of the ester **20a** gave the corresponding carboxylic acid **51** which was reacted with acetic anhydride to yield the oxazino derivative **52**. The oxazino compound **52** was reacted with ammonium acetate, hydrazine hydrate, benzylamine and methyl glycinate to give the pyrimido[4',5':4,5]thieno[2,3-*b*]quinoxaline derivatives **53**-**56**, respectively [33,34] (Scheme 27).

Scheme 27



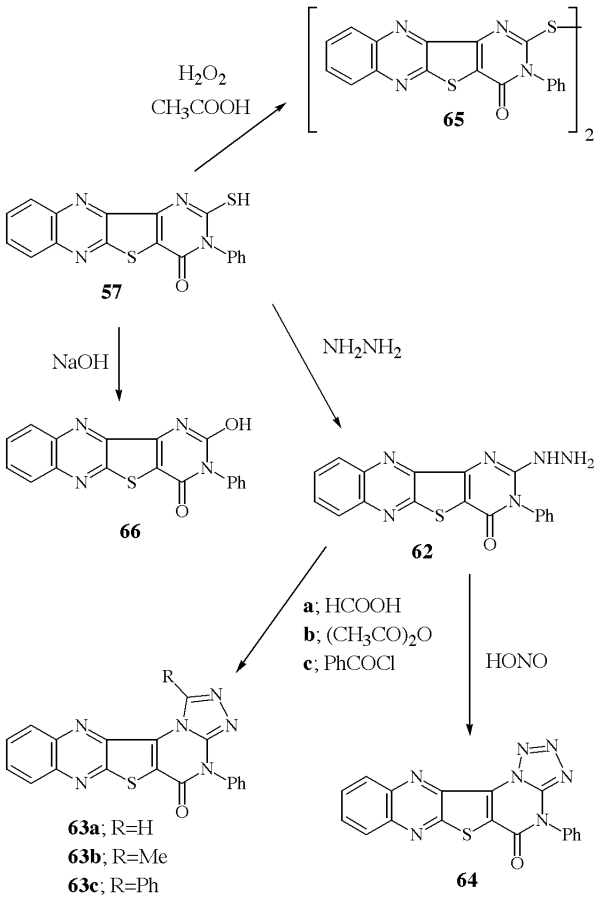
Alkylation of 2-mercapto-3-phenylderivative **57** [14] was carried out with activated reagents such as diethyl bromomalonate, ethyl chloroacetate, chloroacetamide, and phenacylbromide to give *S*-alkyl and *S*-aralkyl derivatives **58-61** [35] (Scheme 28).

Scheme 28



Compound **57** was also reacted with hydrazine hydrate under neat condition to yield the corresponding 2-hydrazino derivative **62** which was cyclized to triazolo derivatives **63a-c** or the tetrazolo compound **64**. Oxidation of **57** by hydrogen peroxide in acetic acid gave the disulfide **65**. Hydroxylation of the thiol **57** with sodium hydroxide gave 2-hydroxy-3-phenylpyrimidothienoquinoxalinone **66** [35] (Scheme 29).

Scheme 29

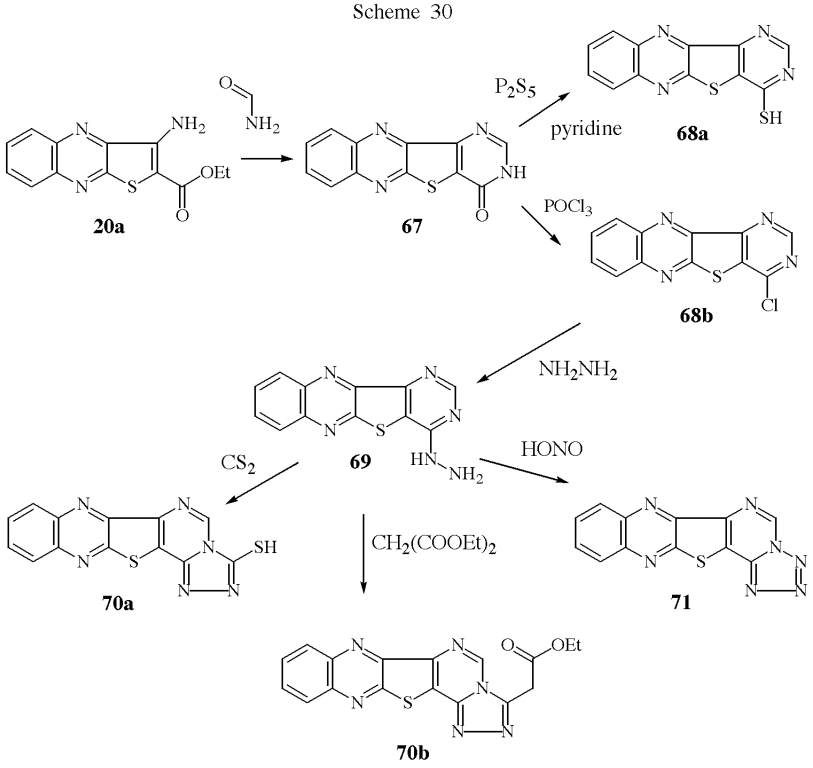


The 4-hydroxypyrimidothienoquinoxaline **67** derived from thieno[2,3-*b*]quinoxaline-2-carboxylate **20a** and formamide was thiolated to **68a** and chlorinated to **68b**, respectively. Treatment of the chloride **68b** with hydrazine produced the hydrazide **69**, which was converted to triazolo derivatives **70a** (using carbon disulfide) and **70b** (using diethyl malonate), and tetrazolo derivative **71** with nitrous acid, respectively [36] (Scheme 30).

The cyclocondensation of 3-aminothieno[2,3-*b*]quinoxaline-2-carbonitrile **20b** with formamide afforded the 4-aminopyrimidothienoquinoxaline **72**, while its reaction with phenyl isothiocyanate gave the 4-imino-2-thione derivative **73** [15] (Scheme 31).

Compound **20b** was reacted with ethylenediamine to afford 3-amino-2-(1*H*-4-imidazolin-2-yl)thieno[2,3-*b*]-quinoxaline **74** which was cyclized to imidazopyrimidothienoquinoxaline **75** by refluxing with triethyl orthoformate [38] (Scheme 32).

Scheme 30



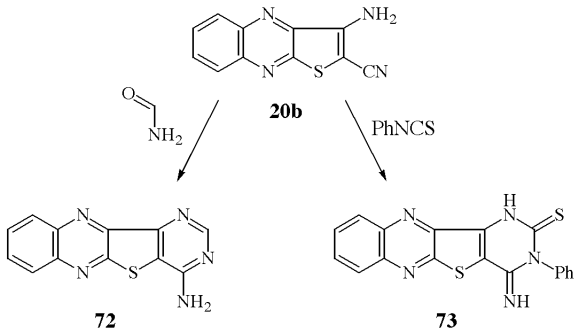
The treatment of thieno[2,3-*b*]quinoxaline-2-carbamide **21** with sodium nitrite in acetic acid afforded the corresponding 1,2,3-triazino[4',5':4,5]thieno[2,3-*b*]quinoxalinone **76**, followed by the thiolation using phosphorus pentasulfide and by the chlorination using phosphorus oxychloride to give the corresponding 4-thio and 4-chloro-1,2,3-triazino compounds **77a**,**b**, respectively.

Furthermore, hydrazinolysis of the chloride **77b** with hydrazine hydrate afforded the 4-hydrazino derivative **78** which was used as a starting material to prepare 1,2,3-triazolo[4",3":1',6'][1,2,3]triazino[4',5':4,5] thieno[2,3-*b*]-quinoxalines **79a**,**b** [37,38] (Scheme 33).

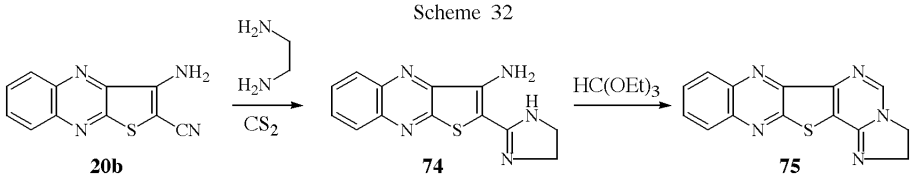
Moreover, β-aminocarboxamide **21** was reacted with sulfuryl and thionyl chloride, acetic anhydride, triethyl orthoformate, and chloroacetylchloride to yield thiadiazino **80**, **81** and pyrimido[4',5':4,5]thieno[2,3-*b*]quinoxalines **83a-c**, respectively [37-39] (Scheme 34).

Bromination of 1,3-dihydrothieno[3,4-*b*]quinoxaline **1c** in dry benzene leads to 1,1,3,3-tetrabromodihydrothienoquinoxaline **84a** which reacted with sodium iodide in acetone to afford 1,3-dibromothieno[3,4-*b*]quinoxaline **85a**. On the other hand, compound **1c** has been reacted under Vilsmeier conditions (phosphoryl chloride/-dimethylformamide) gave 1,3-diformyl-4,9-dihydro derivative **84b** which was oxidized smoothly with iodobenzene diacetate to yield the corresponding aromatic dicarbaldehyde **85b** [4] (Scheme 35).

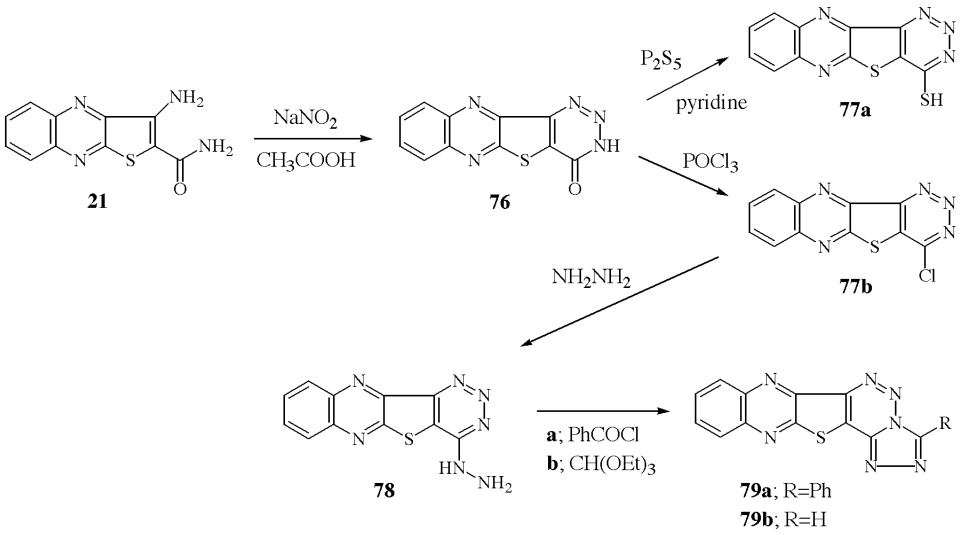
Scheme 31



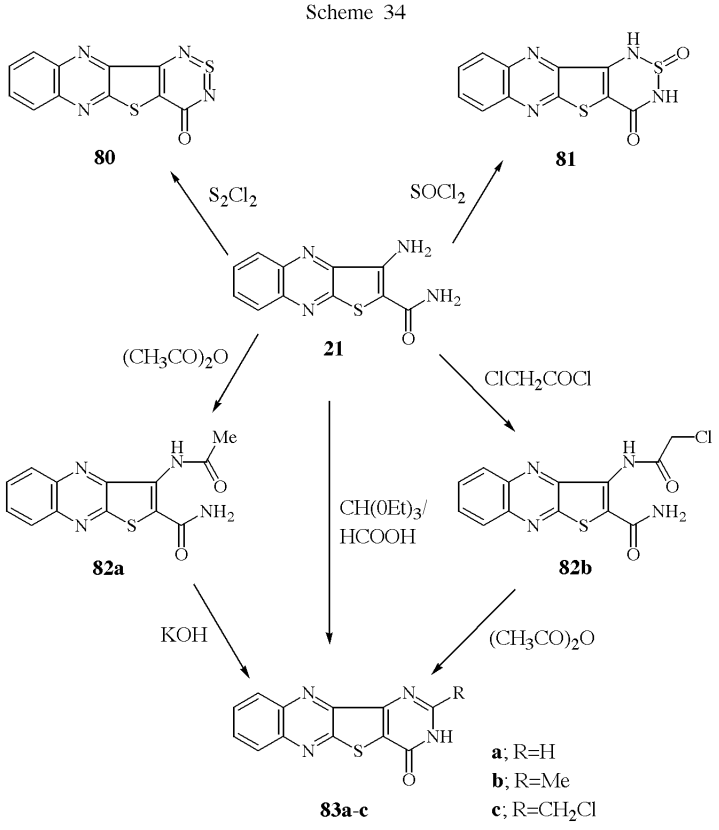
Scheme 32



Scheme 33



Scheme 34



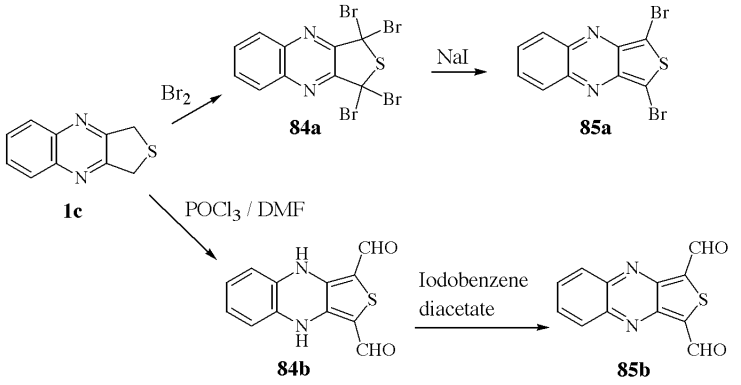
Condensation of dihydrothieno[3,4-*b*]quinoxalines **1c**, **44a** with 2-thienylcarbaldehydes **86a**,**b** in the Knoevengel reaction provided the 1,3-bisthienylmethylenes **87**-**89** [40] (Scheme 36).

Treatment of **1c** with trifluoroacetic acid gave the dimer that was assigned as structure **6** [4] (Scheme 37).

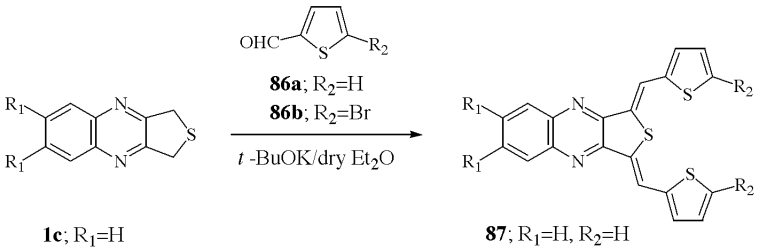
Acylation of 1,3,3a,4,9,9a-hexahydrothieno[3,4-*b*]quinoxaline-2,2-dioxide **9d** by *p*-chlorobenzoylchloride afford the corresponding *N*-acyl product **90** [41, 42] (Scheme 38).

Flash pyrolysis of 1,3-dihydrothieno[3,4-*b*]quinoxaline-2,2-dioxide **5** in benzene at 500 °C followed by addition of excess *N*-phenylmaleimide as a dienophile at -78 °C gave

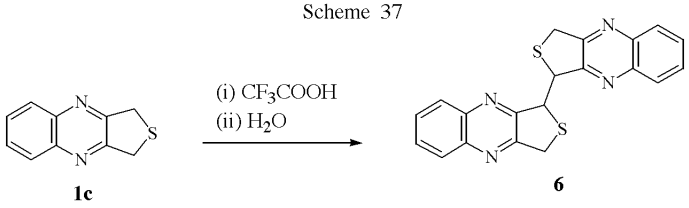
Scheme 35



Scheme 36



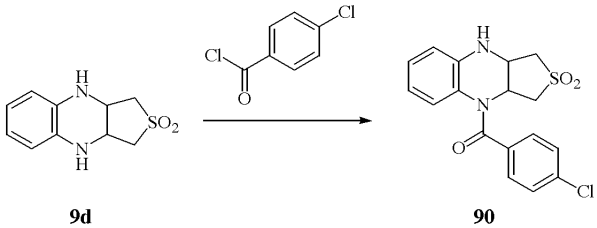
Scheme 37



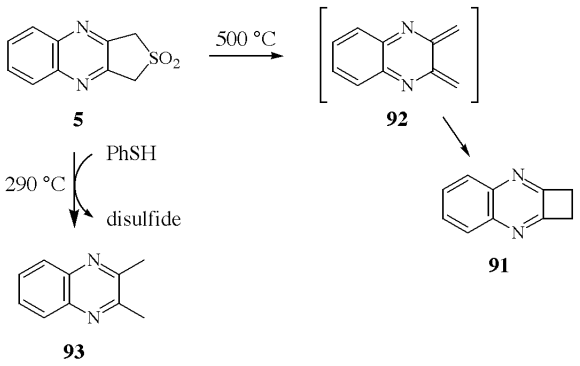
mainly polymerized product. Compound **91** was, however, obtained in low yield (10 %), and it was indicated that **92** should have been a transient intermediate. Thermolysis of **5** at 290 °C in the presence of thiophenol gave 2,3-dimethylquinoxaline **93** [43,44] (Scheme 39).

Compound **5** underwent smooth deprotonation/alkylation reactions [43,44] in relatively lower yields. Tetraalkylated **94**, **95** and trimethylated derivatives **96** were obtained when **5** was treated with excess amount of *n*-butyllithium and alkyliodide. When methyl iodide was used in insufficient amount, the mono- and dimethylated

Scheme 38

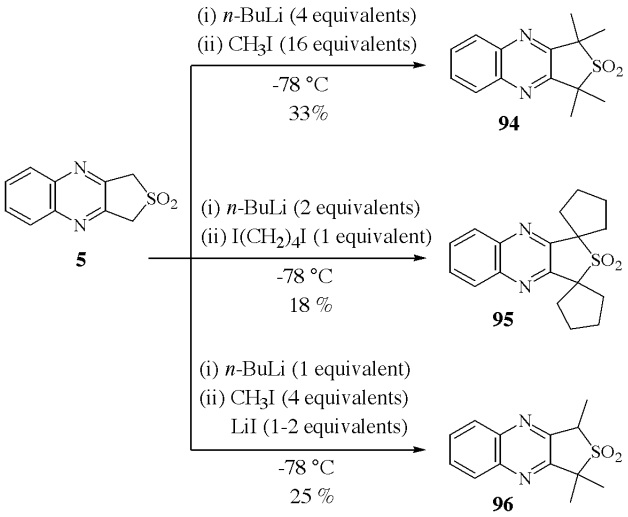


Scheme 39



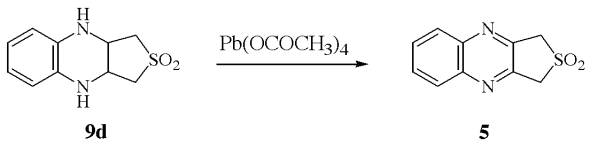
products were obtained as evidenced by nmr analysis, but they could not be isolated. The dissatisfactory results of these methylation reactions might be due to *N*-substitution and salt formation [45] (Scheme 40).

Scheme 40



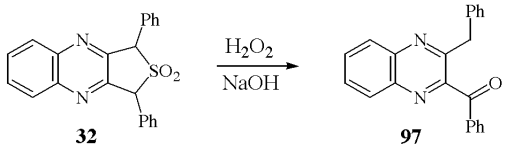
Lead tetraacetate oxidation of hexahydro compound **9d** led to aromatization of the tetrahydropyrazine moiety to afford 1,3-dihydrothieno[3,4-*b*]quinoxaline-2,2-dioxide **5** [6] (Scheme 41).

Scheme 41



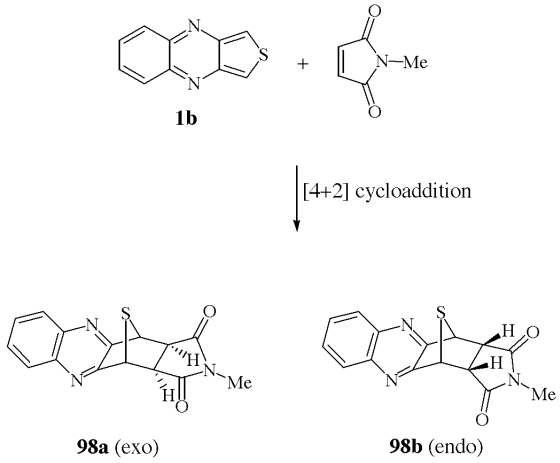
Oxidation of the sulfone **32** with hydrogen peroxide in aqueous ethanolic sodium hydroxide furnished 3-benzoyl-2-benzylquinoxaline **97** as a degradation product in excellent yield [23] (Scheme 42).

Scheme 42



The Diels-Alder reaction of compound **1b** with *N*-methylmaleimide afforded the adducts **98a** (exo) and **98b** (endo). The ratio of exo/endo adducts varies a little due to reaction time and reaction temperature, but the formation of the exo isomer is generally favorable. The structures of **98a** (exo) and **98b** (endo) were assigned on the basis of their ^{1}H-nmr spectra by analogy with the corresponding *N*-phenyl adducts of benzo[*c*]thiophene [46, 47] (Scheme 43).

Scheme 43

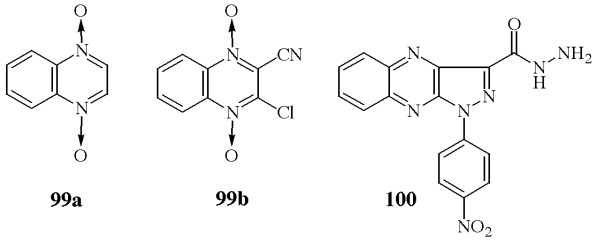


5. Applications of the Quinoxaline Derivatives.

Quinoxaline derivatives have a variety of uses, such as colorimetric reagents for the detection and quantitative estimation of metals [48,49], dyes [50], and even as heat-stable oil additives [51]. Some derivatives of thieno-[3,4-*b*]quinoxaline **1b** were reported to possess analgesic and anti-inflammatory activities [42, 52].

Quinoxalinedioxide derivatives **99a**,**b** and pyrazolo-[3,4-*b*]quinoxaline derivative **100** had been described to be antibacterial agents [53,69], animal growth promotants, and as agents for improving feed efficiency of animals [54-57] (Scheme 44).

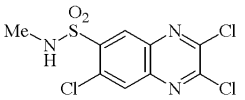
Scheme 44



99a **99b** **100**

A number of quinoxaline derivatives such as 2,3,7-trichloroquinoxaline-6-(yl-*N*-) methylsulfonamide **101** have been patented as anticancer drugs [58, 59,70] (Scheme 45).

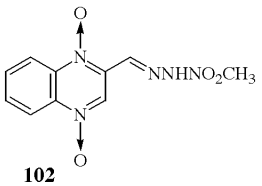
Scheme 45



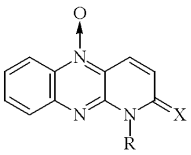
101

Furthermore, other substituted quinoxalines **102**-**105** displayed antiamoebic, antitrichomonal, and antiswine dysenteric properties [27,60-63] (Scheme 46).

Scheme 46

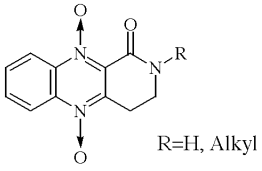


102



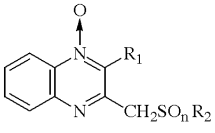
103

X=NH, O
R=Alkyl



R=H, Alkyl

104

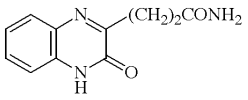


105

n =1, 2
R_1=$COCH_3$, CO_2CH_3
R_2=Alkyl

Also, some derivatives of quinoxalinylpropionamide **106** acted as tranquilizing and antidepressant agents [64] (Scheme 47).

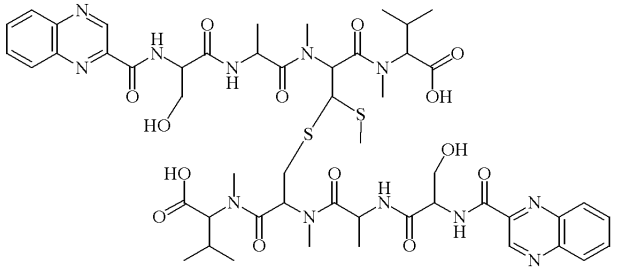
Scheme 47



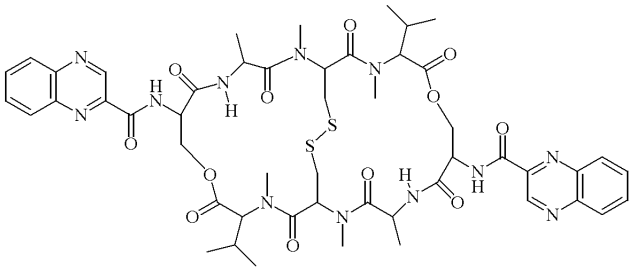
106

A new member of the quinoxaline antibiotics produced by *steroptomyces tenda* is a noncyclic form of Echinoserine **107** [64] and Trisostin A **108**, naturally occurring quinoxaline antibiotics which binds specifically to DNA [65] (Scheme 48).

Scheme 48



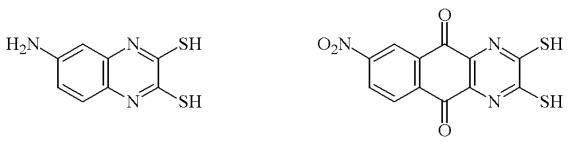
107



108

On the other hand, 2,3-dimercapto-7-aminoquinoxaline **109** and 2,3-dimercapto-8-nitrobenzo[*g*]quinoxaline-5,10-dione (**110**) were prepared as neoplasm inhibitor, fungicide, virucide, and agent for the control of hydrosulfide group (SH) metabolism disturbances [30,67,72] (Scheme 49).

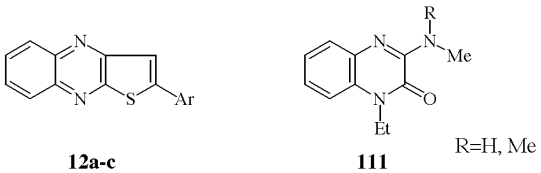
Scheme 49



109 **110**

Recently, some 2-arylthieno[2,3-*b*]quinoxalines **12a-c** were found to have a greater antimicrobial potency [68], while 1-ethyl-3-(*N*-methylamino)quinoxlin-2-ones **111** had antiasthmatic activity [69] (Scheme 50).

Scheme 50



12a-c **111**

6. Conclusion.

The synthetic methodology of thienoquinoxalines from difuctionalized quinoxaline, thiophene ring, and butanedione (**1b**), from unsubstituted quinoxaline (**1a**), from benzothiophene ring (**3a**), and from quinoxaline cyclic dithiol (**7a**) was indicated. A number of the thienoquinoxalines described have been reported to show interesting biological activities. Therefore, these intermolecular cyclization reactions will be further exploited to design new, important, and more complex heterocyclic systems aiming at development of new types of drugs. Furthermore, highly complex heterocycles will be studied in the field of electro chemistry, and in any aspects of spectroscopy. We hope that the present review will be applied to such studies.

Acknowledgement.

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REFERENCES AND NOTES

[1] C. G. Overberger, S. P. Ligthelm, and E. A. Swire, *J. Am. Chem. Soc*., **72**, 2856 (1950).

[2] M. M. Roland and R. C. Anderson, *J. Heterocyclic Chem*., **14**, 541 (1977).

[3] T. S. Chou and C. W. Ko, *Tetrahedron*, **50**, 10721 (1994).

[4] J. Pohmer, M. V. Lakshmikantam, and M. P. Cava, *J. Org. Chem*., **60**, 8283 (1995).

[5] V. M. Ruiz, R. Tapia, J. Valderrama, and J. C. Vega, *J. Heterocyclic Chem*., **18**, 1161 (1981).

[6] J. M. Vierfond, L. Legendre, J. Mahuteau, and M. Miocque, *Heterocycles*, **29**, 141 (1989) .

[7] Y. Mettey, J. M. Vierfond, C. Thal, and M. Miocque, *J. Heterocyclic Chem*., **20**, 133 (1983).

[8] Y. A. Ibrahim, *Chem. Ind. (London)*, **13**, 536 (1980).

[9] Y. A. Ibrahim, M. A. Badawy, and S. El-Bahaie, *J. Heterocyclic Chem.*, **19**, 699 (1982).

[10] E. Lippmann and W. Shilov, *Collect. Czech. Chem. Commun.*, **49**, 1304 (1984); *Chem. Abstr.*, **101**, 191848u (1984).

[11] W. Shilov and E. Lippmann, *Z. Chem*., **26**, 101 (1986); *Chem. Abstr.*, **106**, 138394v (1987).

[12] A. P. Kozynchenko, F. S. Babichev , V. K. Promonenkov, A. I. and L. I. Savranskii, *Ukr. Khim, Zh. (Russ. Ed.*), **53**, 401 (1987); *Chem. Abstr.*, **108**, 167423a (1988).

[13] E. Campaigne and A. R. McLaughlin, *J. Heterocyclic. Chem*., **20**, 623 (1983).

[14] M. Z. A. Badr, S. A. Mahgoub, O. S. Moustafa, and A. A. Geies, *Phosphorus, Sulfur, and Silicon*, **79**, 77 (1993).

[15] S. A. Mahgoub, *Phosphorus, Sulfur, and Silicon*., **61**, 151 (1991).

[16] S. W. Schneller, F. W. Clough, and L. E. Hardee, *J. Heterocyclic Chem*., **13**, 273 (1976).

[17] S. W. Schneller and F. W. Clough, *Heterocycles*, **3**, 135 (1975).

[18] M. J. Haddadin , N. C. Chelhot, and M. Pieridou, *J. Org. Chem*., **39**, 3278 (1974).

[19] T. S. Chou and C. Y. Tsai, *Tetrahedron Lett*., **33**, 4201 (1992).

[20] K. Ando, N. Akadegawa, and H. Takayama, *J. Chem. Soc. Perkin Trans., 1*, 2263 (1993).

[21] J. Toman, J. Klicnar, and S. Kalabova, *Khim. Geterosikl. Soedin*., **3**, 352 (1987); *Chem. Abstr*., **108**, 37782f (1988).

[22] W. Ott, E. Ziegler and G. Kollenz, *Synthesis*, 477 (1976).

[23] K. Peters, E. M. Peters, H. G. Schnering, G. Kollenz, E. Terpetschnig, and W. Ott, *Z. Kristallogra.*, **177**, 301 (1986).

[24] J. M. Bolster and R. M. Kellogg, *J. Org. Chem*., **47**, 4429 (1982).

[25] E. J. Moriconi, R. E. Misner, and T. E. Brady, *J. Org. Chem*., **34**, 1651 (1969).

[26] B. Venugopalan, C. P. Bapat, N. J. de Souza, D. K. Chatterjee, and N. J. Iyer, *Eur. J. Med. Chem*., **24**, 611 (1989).

[27] B. Venugopalan, C. P. Bapat, D. K. Chatterjee, N. J. de Souza, and H. R. Rupp, *Indian, IN* 167,425 (1990); *Chem. Abstr*., **119**, 117279q (1993).

[28] K. D. Banerji, A. K. D. Mazumdar, and K. K. Sen, *J. Indian Chem. Soc.*, **50**, 268 (1973).

[29] E. J. Moriconi and A. J. Fritsch, *J. Org. Chem*., **30**, 1542 (1965).

[30] N. Muresan and V. E. Muresan, *Rom.*, *RO* 88,071 (1985); *Chem. Abstr.*, **105**, 115095p (1986).

[31] W. F. Gray, I. H. Pomerantz, and R. D. Ross, *J. Heterocyclic Chem*., **9**, 707 (1972).

[32] M. Z. A. Badr, S. A. Maghoub, O. S. Moustafa, and F. M. Abd El-Latif, *J. Chem. Soc. Pakistan*, **15**, 264 (1993); *Chem. Abstr.*, **121**, 9333k (1994).

[33] S. W. Schneller and F. W. Clough, *J. Heterocyclic Chem*., **12**, 513 (1975).

[34] M. Z. A. Badr, S. A. Mahgoub, A. A. Geies, O. S. Moustafa, and F. M. Abd El-Latif, *Phosphorus, Sulfur, and Silicon*, **73**, 27 (1992).

[35] O. S. Moustafa and M. Z. A. Badr, *Phosphorus, Sulfur, and Silicon.*, **119**, 127 (1996).

[36] M. Z. A. Badr, S. A. Mahgoub, F. M. Atta, and O. S. Moustafa, *J. Indian Chem. Soc*., **74**, 30 (1997).

[37] O. S. Moustafa, *Phosphorus, Sulfur, and Silicon*, **131**, 49 (1997).

[38] O. S. Moustafa, *Phosphorus, Sulfur, and Silicon*, **155**, 235 (1999).

[39] W. Offermann, K. Eger, and H. J. Roth, *Arch. Pharm*., **314**, 168 (1981).

[40] G. Hieber, M. Hanack, K. Wurst, and J. Strahle, *Chem. Ber.*, **124**, 1597 (1991).

[41] N. Hainder and H. C. van der Plas, *Tetrahedron*, **46**, 3641 (1990).

[42] J. M. Vierfond, L. Legendre, C. Martin, P. Rinjard, and M. Miocque, *Eur. J. Med. Chem*., **25**, 251 (1990).

[43] T. S. Chou and H. H. Tso, *Org. Prep. Proc. Int*., **21**, 257 (1989).

[44] T. S. Chou and S. P. Chou, *J. Chin. Chem. Soc*., **39**, 625 (1992).

[45] V. N. Charushin, O. N. Chupakhin, and H. C. van der Plas, *Adv. Heterocyclic Chem.*, **43**, 301 (1988).

[46] M. P. Cava and N. M. Pollack, *J. Am. Chem. Soc*., **88**, 4112 (1966).

[47] M. P. Cava, N. M. Pollack, O. A. Mamer, and M. J. Mitchell, *J. Org. Chem*., **36**, 3932 (1971).

[48] L. J. Theriot, K. K. Canguli, S. Kavarnos, and I. Bernal, *J. Inorg. Nucl. Chem*., **31**, 3133 (1969); *Chem. Abstr*., **71**, 112888t (1969).

[49] G. H. Ayres and H. F. Janota, *Anal. Chem*., **31**, 1985 (1959); *Chem. Abstr*., **54**, 10666c (1960).

[50] G. W. H. Cheeseman and E. S. G. Werstiuk, *Adv. Heterocyclic. Chem*., **22**, 367 (1978).

[51] D. Boutte and S. Lecolier, *Fr. Demande*, 2,249,289 (1975); *Chem. Abstr*., **84**, 138243x (1976).

[52] G. C. I. Moore, J. K. Harrington, and K. F. Swingle, *Eur. J. Med. Chem*., **18**, 386 (1975).

[53] H. S. Kim, J. Y. Chung, E. K. Kim, Y. T. Park, Y. S. Hong, M. K. Lee, Y. Kurasawa, and A. Takada, *J. Heterocyclic Chem.*, **33**, 1855 (1996).

[54] G. W. Thrasher, J. E. Shively, C. E. Askelson, W. E. Babcock, and R. R. Chalquest, *J. Anim. Sci*., **28**, 208 (1969); *Chem. Abstr*., **70**, 75593z (1969).

[55] J. P. Dirlam and J. E. Presslitz, *J. Med. Chem*., **21**, 483 (1978).

[56] J. P. Dirlam, L. J. Czuba, B. W. Dominy, R. B. James, R. M. Pezzullo, J. E. Presslitz, and W. W. Windisch, *J. Med. Chem*., **22**, 1118 (1979).

[57] A. J. Barker, A. M. Vega, and E. Hamilton, *Brit. UK Pat. Appl., GB* 2,297,089 (1996); *Chem. Abstr.*, **125**, 247851s (1996).

[58] G. Sakata, K. Makino, and Y. Kurasawa, *Heterocycles*, **27**, 2481 (1988).

[59] M. Loriga, S. Piras, P. Sanna, and G. Paglietti, *Farmaco*, **52**, 157 (1997); *Chem. Abstr*., **127**, 205547w (1997).

[60] E. A. Glazer and L. R. Chappel, *J. Med. Chem*., **25**, 766 (1982).

[61] E. A. Glazer and L. R. Chappel, *J. Med. Chem*., **25**, 868 (1982).

[62] J. P. Dirlam, J. E. Presslitz, and B. J. Williams, *J. Med. Chem*., **26**, 1122 (1983).

[63] B. Venugopalan, S. S. Iyer, P. J. Karnik, and N. J. de Souza, *Heterocycles*, **26**, 3173 (1987).

[64] T. O. Yellin, *U. S. Pat.*, 3,635,971 (1972); *Chem. Abstr*., **76**, 99708r (1972).

[65] S. Blum, H. P. Fielder, I. Groth, C. Kempter, H. Stephan, G. Nicholson, J. W. Metzger, and G. Jung, *J. Antibiot.*, **48**, 619 (1995); *Chem. Abstr.*, **123**, 164756k (1995).

[66] K. J. Addess and J. Feigon, *Biochemistry*, **33**, 12386 (1994).

[67] N. Muresan and V. E. Muresan, *Rom.*, *RO* 88,072 (1985); *Chem. Abstr*., **105**, 115096q (1986).

[68] T. N. Yanborisov, N. N. Kasimova, O. A. Yanborisova, and I. A. Zhikina, Y. S. Andreichikov, G. N. Novoselova, and A. V. Milyutin, *Khim.-Farm. Zh*., **30**, 31 (1996); *Chem. Abstr*., **125**, 157865h (1996).

[69] J. F. Patoisear, J. P. Tarayre, and J. M. Autin, *PCT Int. Appl., WO* 96 26,928 (1996); *Chem. Abstr*., **125**, 275913v (1996).

[70] K. Makino, H. S. Kim, and Y. Kurasawa, *J. Heterocyclic Chem.*, **36**, 321 (1999).

[71] H. W. Yoo, Y. S. Lee, M. E. Suh, D. J. Kim, and S. W. Park, *Arch. Pharm.*, **331**, 331 (1998).

[72] W. Lunkenheimer and K. H. Buechel, *Ger. Offen,*, 2,342,724 (1975); *Chem. Abstr*., **82**, 156379 (1975).