Synthesis and Biological Activity of 1,5-Dihydropyridazino-[3,4-*b*]quinoxalines and a New Class of Quinolones

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A new class of quinolones, 1,4-dihydro-4-oxopyridazino[3,4-*b*]quinoxaline-3-carboxylic acids and related compounds, were synthesized *via* oxidation of 1,5-dihydropyridazino[3,4-*b*]quinoxalines obtained from 2-hydrazinoquinoxaline 4-oxides. Some of the 1,5-dihydropyridazino[3,4-*b*]quinoxalines, 1,4-dihydro-4-oxopyridazino[3,4-*b*]quinoxaline-3-carboxylic acids, and related compounds showed biological activity.

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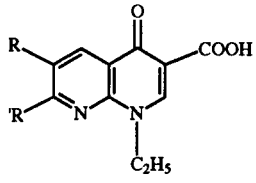
Introduction.

Since the discovery of nalidixic acid (Figure 1) in 1962 [1] and its introduction in the treatment of urinary tract infections in 1963, many research groups have developed a new class of quinolone antibacterials [2] including enoxacin [3], oxolinic acid [2], resoxacin [2], pipemidic acid [2], ofloxacin [4], and some other new quinolones [2]. Cinoxacin [2,5] and pyrimido[4,5-*c*]pyridazines [2,6] having a pyridazine moiety have also been synthesized as analogues of nalidixic acid. On the other hand, 1,4-dihydro-4-oxopyrido[2,3-*b*]quinoxaline-3-carboxylic acids (Figure 2) have been synthesized and found to possess bactericidal activity [7], but 1,4-dihydro-4-oxopyridazino-[3,4-*b*]quinoxaline-3-carboxylic acids have not been synthesized yet. In continuation of our investigation on pyridazine synthesis, we found a facile method for the synthesis of 1,4-dihydro-4-oxopyridazino[3,4-*b*]quinoxaline-3-carboxylic acids and related compounds. In the present symposium, we report the synthesis of various pyridazino[3,4-*b*]quinoxalines, 1,4-dihydro-4-oxopyridazino[3,4-*b*]quinoxaline-3-carboxylic acids, and related compounds together with their biological activity.

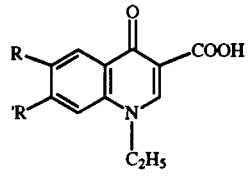
1,8-Naphthyridine



Nalidixic Acid
R = H, R' = CH_3

Enoxacin
R = F, R' = 1-Piperazinyl

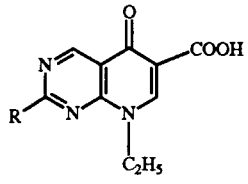
Quinolone



Oxolinic Acid
R, R' = OCH_2O

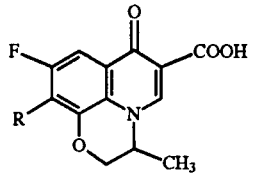
Resoxacin
R = H, R' = 4-Pyridyl

Pyrido[2,3-*d*]pyrimidine



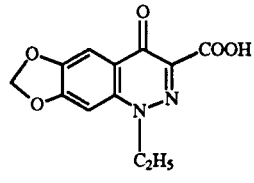
Pipemidic Acid
R = 1-Piperazinyl

Pyrido[1,2,3-*de*][1,4]benzoxazine



Ofloxacin
R = 4-Methyl-1-piperazinyl

Cinnoline



Cinoxacin

Pyrimido[4,5-*c*]pyridazine

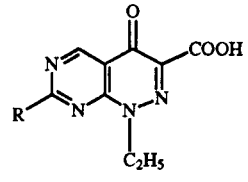
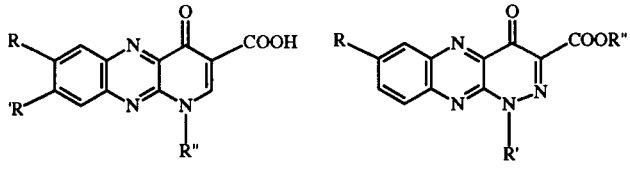


Figure 1.



Pyrido[2,3-*b*]quinoxalines Pyridazino[3,4-*b*]quinoxalines

Figure 2.

I. Synthesis of Pyridazino[3,4-*b*]quinoxalines.

I-1. *Via* the Diazotization.

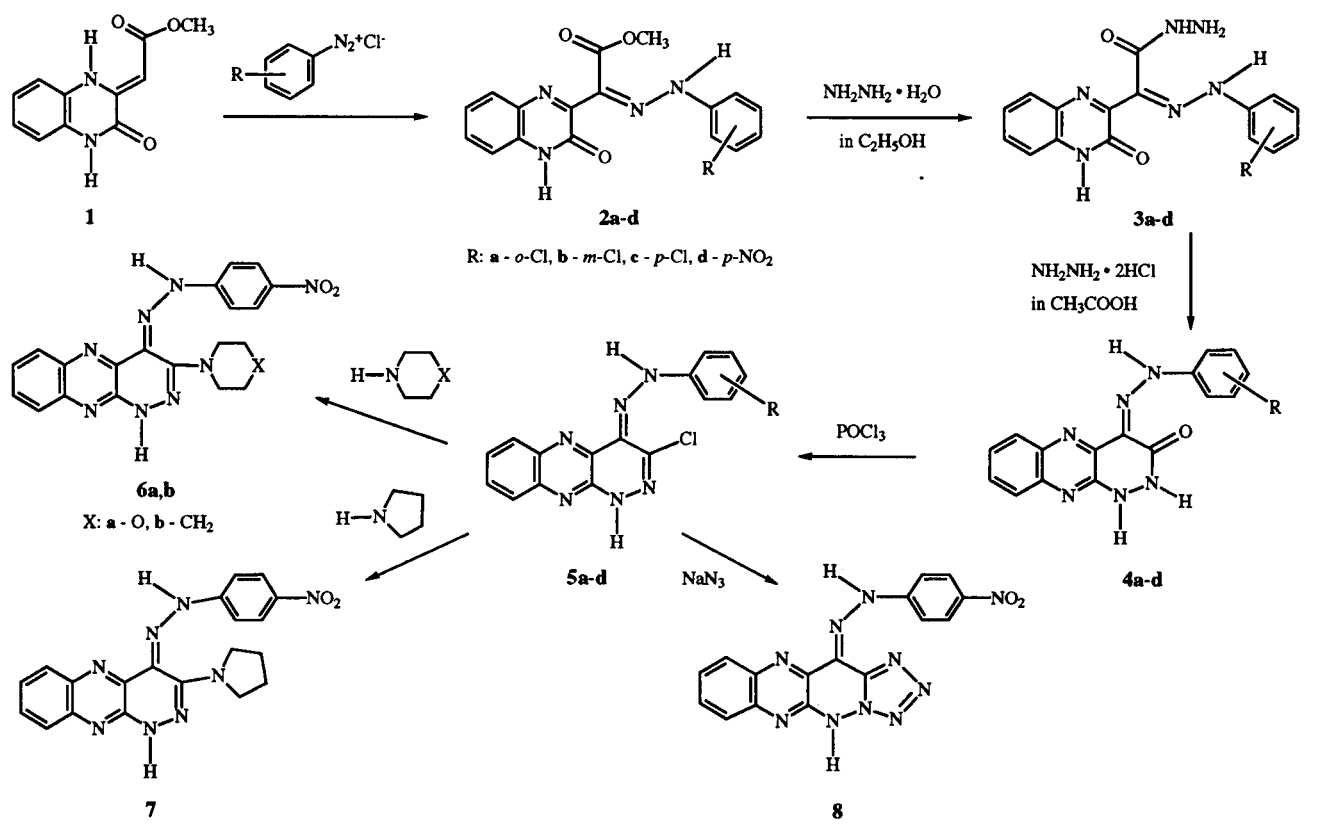
The reaction of the side-chained quinoxaline **1** [8] with the substituted benzenediazonium chlorides gave the hydrazonyl esters **2a-d**, whose reaction with hydrazine hydrate afforded the hydrazonyl acyl hydrazides **3a-d**, respectively (Scheme 1) [9,10]. The reaction of compounds **3a-d** with hydrazine dihydrochloride provided the pyridazino[3,4-*b*]quinoxalin-3-ones **4a-d**, whose chlorination gave the 3-chloropyridazino[3,4-*b*]quinoxalines **5a-d**, respectvely. The *p*-nitro derivative **5d** was converted into the 3-(morpholin-4-yl) **6a**, 3-(piperidin-1-yl) **6b**, and 3-(pyrrolidin-1-yl) **7** derivatives and the tetrazolo-[1',5':1,6]pyridazino[3,4-*b*]quinoxaline **8** [10].

I-2. *Via* Ring Transformation.

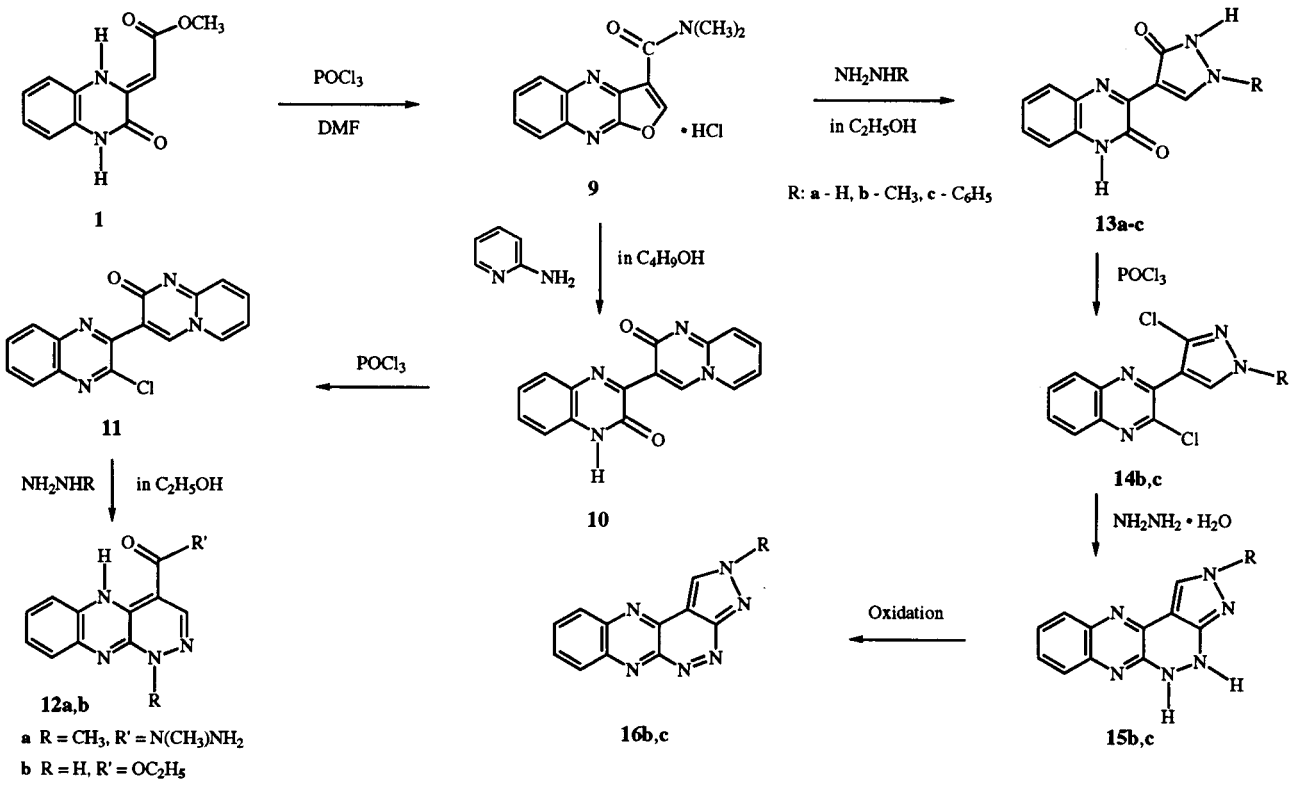
The reaction of compound **1** with the Vilsmeier reagent gave the furo[2,3-*b*]quinoxaline-3-carboxamide **9**, whose reaction with 2-aminopyridine resulted in ring transformation to afford the 3-(quinoxalin-3-yl)pyrido[1,2-*a*]pyrimidin-2-one **10** [11,12]. The chlorination of compound **10** with phosphoryl chloride provided the 3-(2-chloroquinoxalin-3-yl)pyrido[1,2-*a*]pyrimidin-2-one **11**, whose reaction with methylhydrazine or hydrazine hydrate in ethanol effected ring transformation to give the 4-(hydrazinocarbonyl)pyridazino[3,4-*b*]quinoxaline **12a** or ethyl pyridazino[3,4-*b*]quinoxaline-4-caboxylate **12b**, respectively.

On the other hand, the reaction of the furo[2,3-*b*]quinoxaline-3-carboxamide **9** with hydrazine hydrate, methylhydazine, and phenylhydrazine resulted in ring transformation to afford the 3-(pyrazol-4-yl)quinoxalin-2-ones **13a-c**, respectively [13,14]. The reaction of compounds **13b,c** with phosphoryl chloride provided the 2-chloro-3-(3-chloropyrazol-4-yl)quinoxalines **14b,c**, whose reaction with hydrazine hydrate produced the 4,5-dihydropyrazolo[3',4':3,4]pyridazino[5,6-*b*]quinoxalines **15b,c**, respectively. Oxidation of compounds **15b,c** with azodicarboxylate or under aeration gave compounds **16b,c**, respectively.

Scheme 1



Scheme 2



I-3. *Via* a 1,3-Dipolar Cycloaddition Reaction.

The reaction of 2,6-dichloroquinoxaline 4-oxide **17** with methylhydrazine or hydrazine hydrate afforded 6-chloro-2-(1-methylhydrazino)quinoxaline 4-oxide **18** or 6-chloro-2-hydrazinoquinoxaline 4-oxide **19**, respectively (Scheme 3) [15,16]. The reaction of compound **18** with dimethyl or diethyl acetylenedicarboxylate provided the 1,5-dihydropyridazino[3,4-*b*]quinoxaline **20a** or **20b**, respectively, presumably *via* intermediates **A-D**, while the reaction of compound **19** with dimethyl acetylenedicarboxylate produced the hydrazone **21**.

On the other hand, the reaction of 2,6-dichloroquinoxaline **22** with peroxysulfuric acid gave 2,6-dichloroquinoxaline 1-oxide **23**, whose reaction with methylhydrazine afforded 6-chloro-2-(1-methylhydrazino)quinoxaline 1-oxide **24** (Scheme 4) [17]. The reaction of compound **24** with dimethyl or diethyl acetylenedicarboxylate provided the dimethyl or diethyl 8-chloro-1-methylpyridazino-[3,4-*b*]quinoxaline-3,4-dicarboxylate **25a** or **25b**, respectively, presumably *via* intermediates **E-G**.

I-4. *Via* the Addition of β-Diketones or β-Ketoesters to the α-Carbon of the *N*-Oxide Moiety.

The reaction of the quinoxaline *N*-oxide **18** with β-diketones (acetylacetone and benzoylacetone) and β-ketoesters (ethyl and methyl acetoacetates) gave the 4-substituted 7-chloro-1,3-dimethylpyridazino[3,4-*b*]quinoxalines **26a-d**, respectively, presumably *via* intermediates **H** and **I** (Scheme 5) [18].

The reaction of compound **18** with diethyl acetonedicarboxylate or 1,3-cyclohexanedione also afforded the pyridazino[3,4-*b*]quinoxaline **28a** or quinoxalino[2,3-*c*]-cinnoline **29a**, respectively (Scheme 6). The ethyl derivative **27** was similarly transformed into compound **28b** or **29b**.

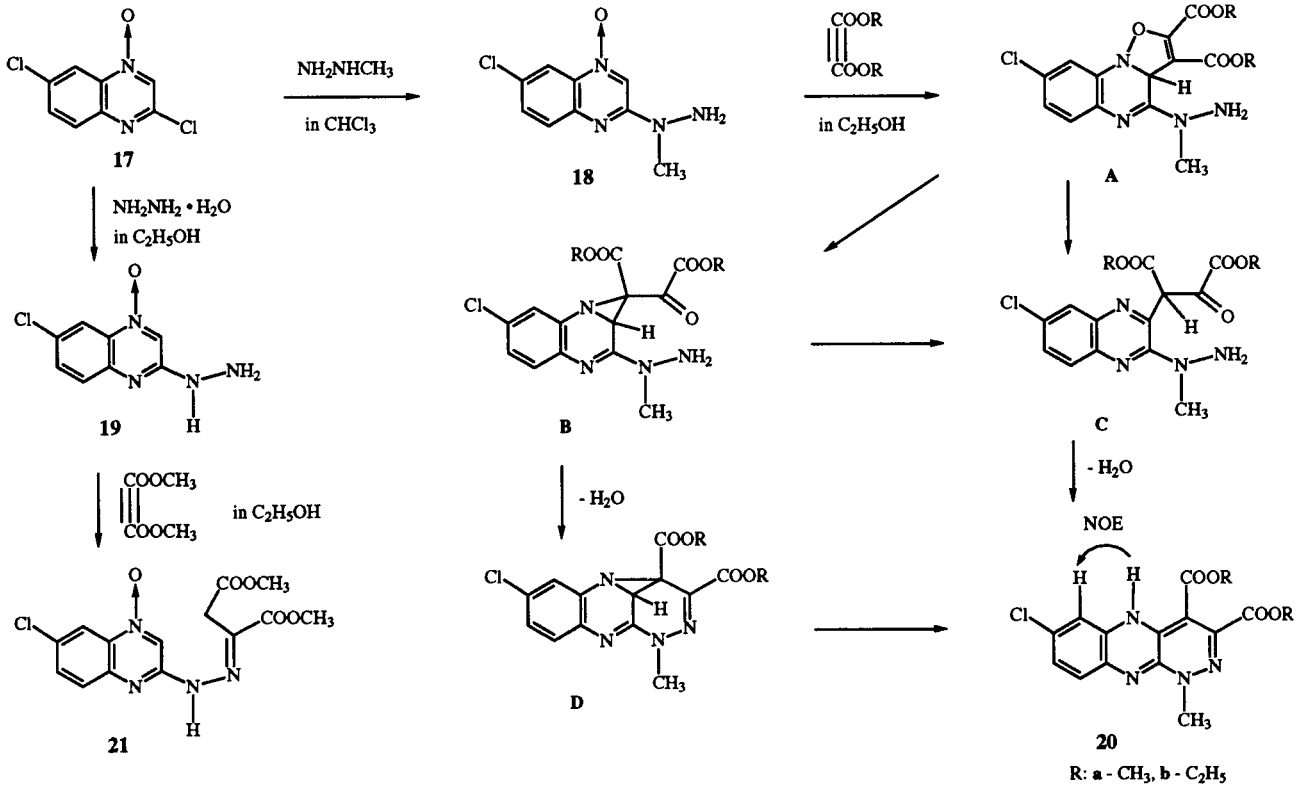
The reaction of quinoxaline *N*-oxide **18** with ethoxymethylenecyanoacetate or ethoxymethylenemalononitrile provided the 2-[1-methyl-2-(substituted)cyanovinylhydrazino]quinoxaline 4-oxide **30a** or **30b**, respectively (Scheme 7) [19]. Reflux of compound **30a** (R = $COOC_2H_5$) in 1,8-diazabicyclo[5.4.0]-7-undecene/*N*,*N*-dimethylformamide gave the pyridazino[3,4-*b*]quinoxaline-4-carbonitrile **31** presumably *via* intermediates **J-L**, while compound **30b** was not converted into a pyridazino-[3,4-*b*]quinoxaline ring.

II. Synthesis of a New Class of Quinolones [20].

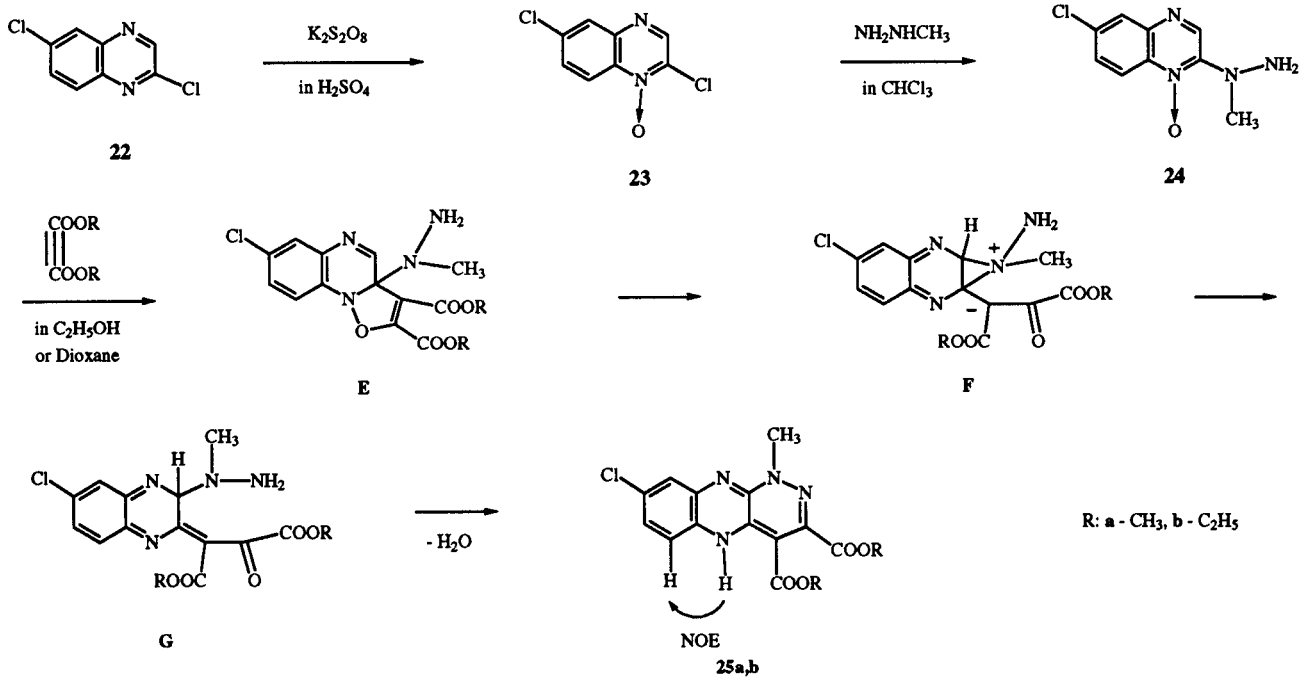
II-1. 1,4-Dihydro-4-oxopyridazino[3,4-*b*]quinoxaline-3-carboxylic Acids and Related Compounds.

The pyridazino[3,4-*b*]quinoxaline-3,4-dicarboxylate **20a** or **32** was found to be oxidized easily with *m*-chloroperbenzoic acid or nitrous acid to give the 4-hydroxy-

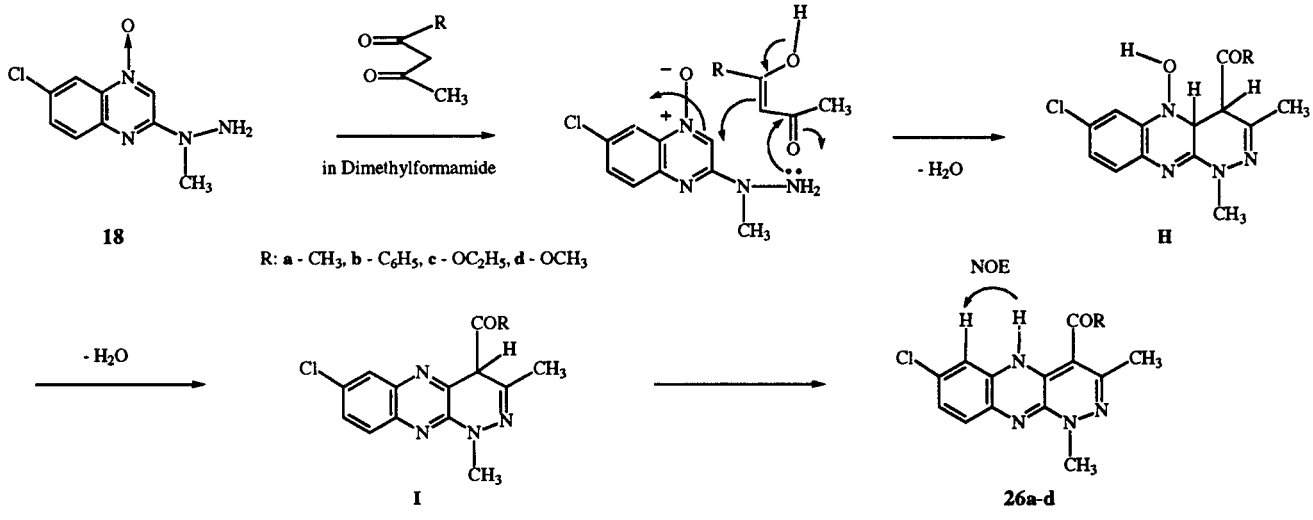
Scheme 3



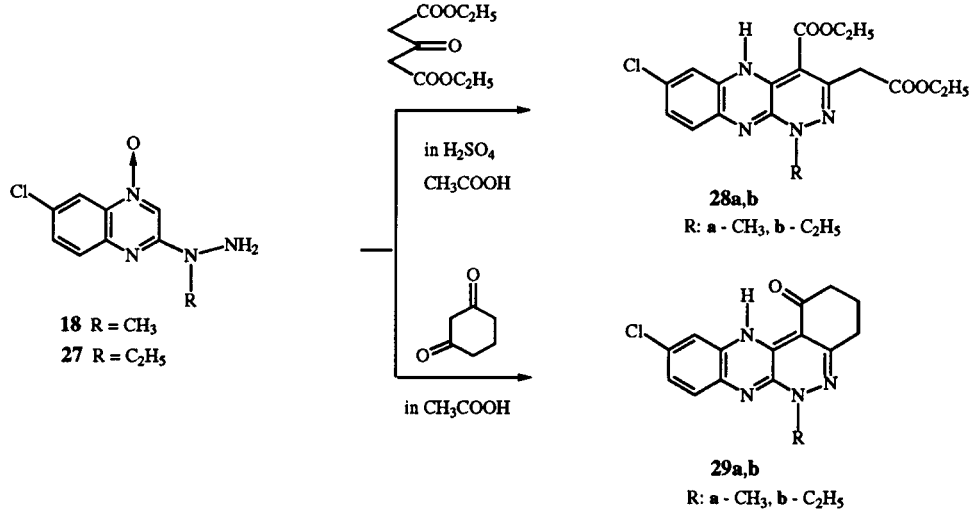
Scheme 4



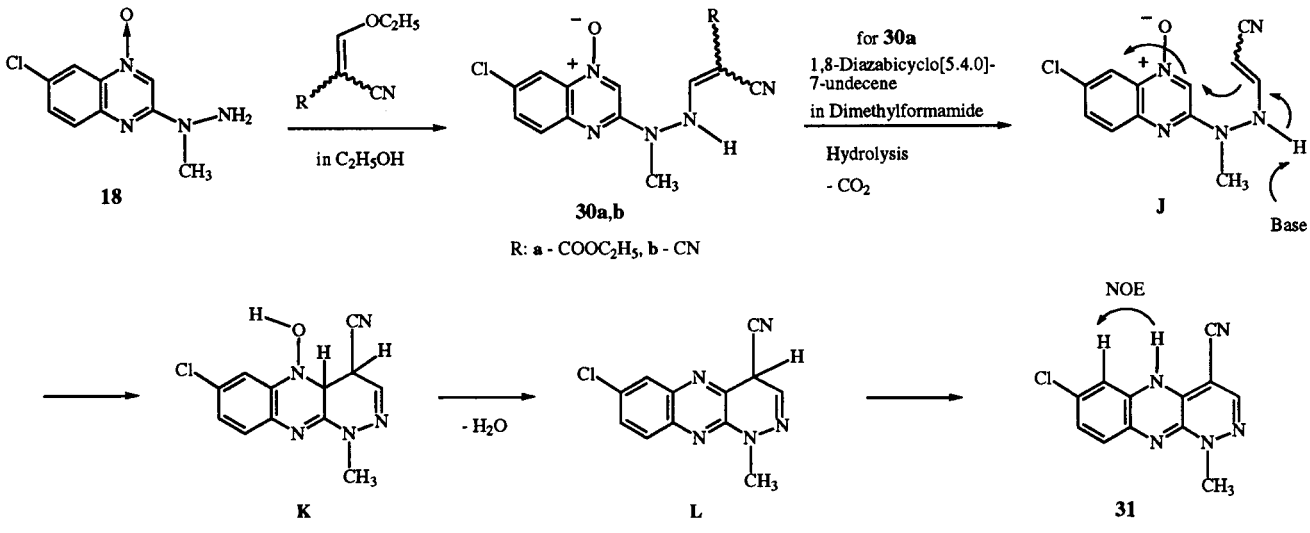
Scheme 5



Scheme 6



Scheme 7

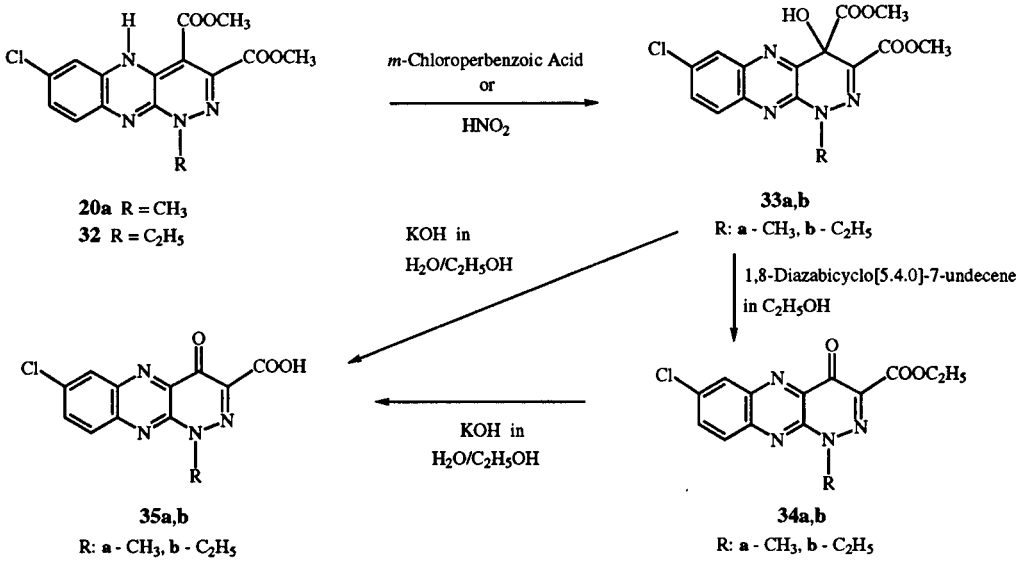


pyridazino[3,4-*b*]quinoxaline-3,4-dicarboxylate **33a** or **33b** (Scheme 8), respectively. The reaction of compounds **33a,b** with 1,8-diazabicyclo[5.4.0]-7-undecene in ethanol afforded the ethyl 1,4-dihydro-4-oxopyridazino[3,4-*b*]-quinoxaline-3-carboxylates **34a,b**, whose hydrolysis with potassium hydroxide provided the 1,4-dihydro-4-oxo-pyridazino[3,4-*b*]quinoxaline-3-carboxylic acids **35a,b**, respectively. The reaction of compounds **33a,b** with potassium hydroxide directly produced compounds **35a,b**, respectively.

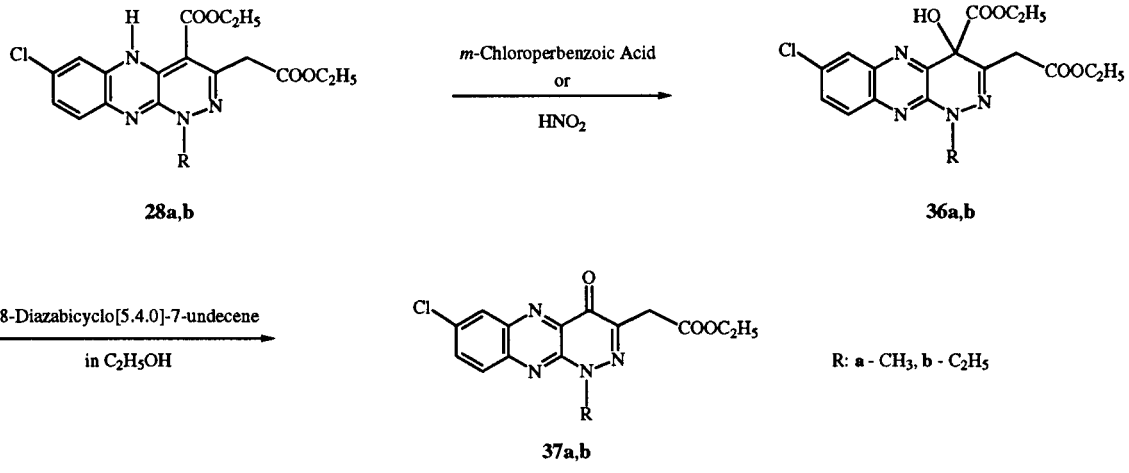
II-2. Ethyl 2-(1,4-Dihydro-4-oxopyridazino[3,4-*b*]quinox-aline-3-yl)acetates.

The reaction of the pyridazino[3,4-*b*]quinoxalines **28a,b** with *m*-chloroperbenzoic acid or nitrous acid gave the 4-hydroxypyridazino[3,4-*b*]quinoxalines **36a,b**, respectively (Scheme 9). The reaction of compounds **36a,b** with 1,8-diazabicyclo[5.4.0]-7-undecene afforded the 2-(1,4-dihydro-4-oxopyridazino[3,4-*b*]quinox-alin-3-yl)acetates **37a,b**, respectevely.

Scheme 8



Scheme 9

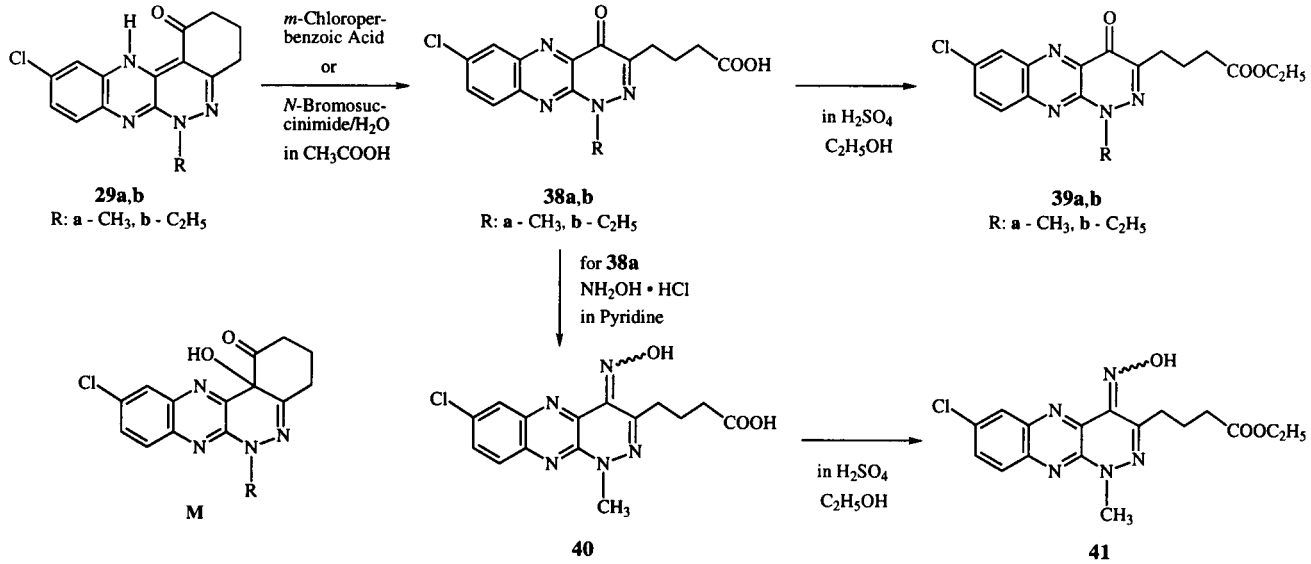


28a,b **36a,b** **37a,b**

II-3. 4-(1,4-Dihydro-4-oxopyridazino[3,4-*b*]quinoxalin-3-yl)butyric Acids and Related Compounds.

The reaction of the quinoxalino[2,3-*c*]cinnolines **29a,b** with *N*-bromosuccinimide/water resulted in the cleavage of the C_1-C_{12b} bond to provide the 4-(1,4-dihydro-4-oxopyridazino[3,4-*b*]quinoxalin-3-yl)butyric acid **38a,b**, whose reflux in concentrated sulfuric acid/ethanol produced the ethyl esters **39a,b**, respectively (Scheme 10). The reaction of compound **38a** (R = CH_3) with hydroxylamine gave the 4-(4-hydroxyimino-1,4-dihydropyridazino[3,4-*b*]quinoxalin-3-yl)butyric acid **40**, whose esterification in concentrated sulfuric acid/ethanol afforded the ethyl ester **41**.

Scheme 10



29a,b R: a - CH_3, b - C_2H_5

38a,b R: a - CH_3, b - C_2H_5

39a,b R: a - CH_3, b - C_2H_5

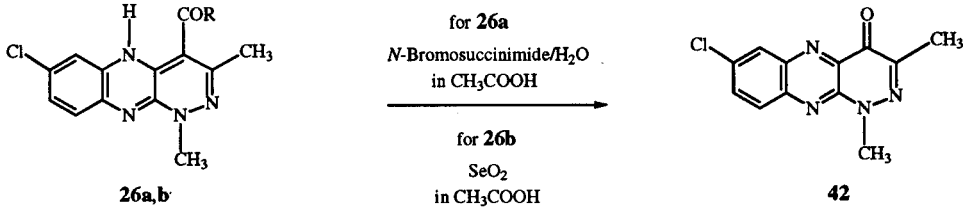
M

40

41

The following tendency was observed for the C_4-oxidation of the pyridazino[3,4-*b*]quinoxalines. When there is an ester group in the C_4-position (compounds **20a**, **28a,b**, **32**), the C_4-hydroxylation was achieved with *m*-chloroperbenzoic acid or nitrous acid (Schemes 8, 9). On the other hand, when there is an acyl group in the C_4-position (compounds **26a,b**), the C_4-oxidation was accomplished with *N*-bromosuccinimide/water or selenium dioxide (Scheme 11), while compounds **29a,b** were oxidized with *m*-chloroperbenzoic acid, *N*-bromosuccinimide (Scheme 10), or sodium bromate (Scheme 12). On the contrary, the oxidation of the C_4-ester or C_4-acyl derivatives was ineffective with *N*-bromosuccinimide/water or nitrous acid, respectively.

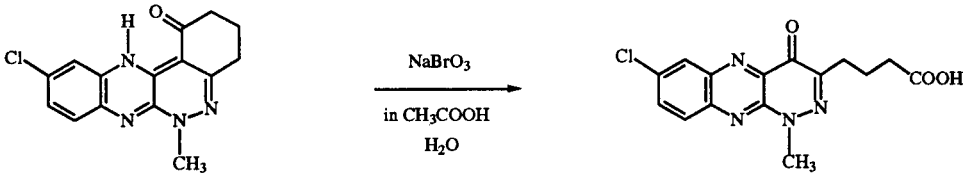
Scheme 11



26a,b
R: **a** - CH_3, **b** - C_6H_5

42

Scheme 12



29a

38a

II-4. 3-Aryl-1,4-dihydro-4-oxopyridazino[3,4-*b*]quinoxalines.

The reaction of compound **18** with aldehydes gave the hydrazones **43a,b**, whose reaction with 2-chloroacrylonitrile afforded the 1,2-diazepino[3,4-*b*]quinoxalines **44a,b**, respectively (Scheme 13) [21,22]. The reaction of compounds **44a,b** with *N*-bromosuccinimide/water resulted in ring transformation to provide the 3-aryl-1,4-dihydro-4-oxopyridazino[3,4-*b*]quinoxalines **46a,b**, respectively, presumably *via* intermediates **N-Q** [23].

III. Biological Activity of Pyridazino[3,4-*b*]quinoxalines.

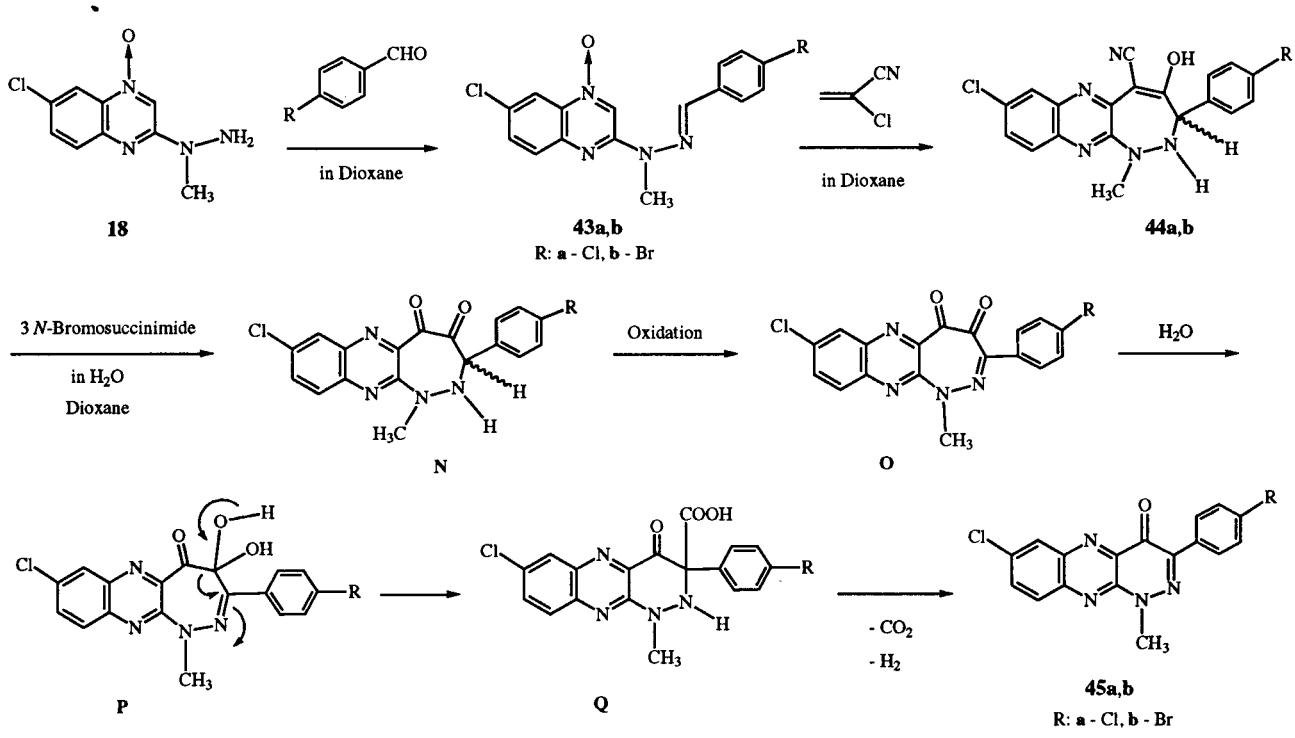
III-1. Antimicrobial Activity.

Compound **34b** exhibited a fungicidal activity to plant disease fungi *Pythium debaryanum (P. d.)*, *Phytophthora infestans (P. i.)*, *Pyricularia oryzae (P. o.)*, *Botrytis cinerea (B. c.)*, and *Rhizoctonia solani (R. s.)*, while compounds **37a,b** or **34a** showed a fungicidal activity to *P. i.* or to *P. i.* and *P. o.*, respectively. Compound **34b** also exhibited bactericidal activity to *Bacillus subtilis*, which was stronger than that of compound **35a** or **36b**. Compounds **37a,b** showed fungicidal activity to *Trichophyton mentagrophytes*.

III-2. Algicidal Activity.

Compounds **34c** and **28a,b** showed algicidal activity to both *Selenastrum capricornutum (S. c)* and *Nitzschia closterium (N. c.)*, while compounds **29a,b** exhibited an algicidal activity to *N. c.*

Scheme 13



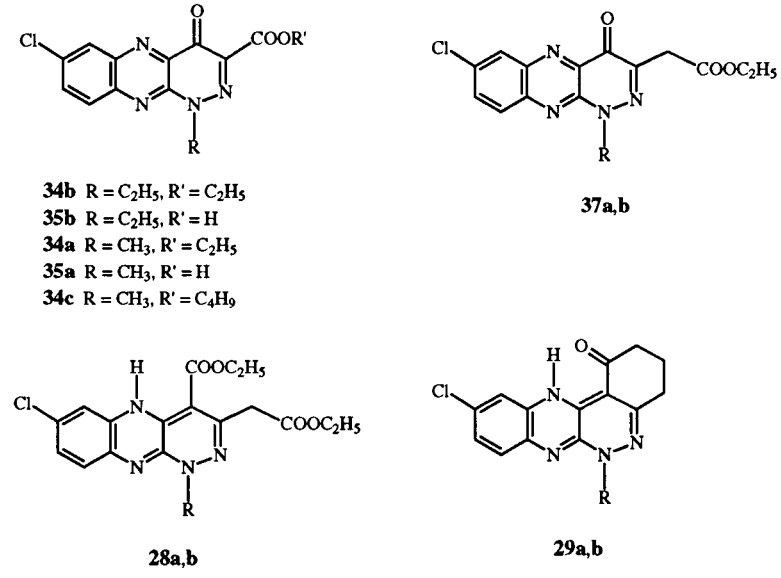


Figure 3.

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