RECENT PROGRESS IN THE QUINOXALINE CHEMISTRY. SYNTHESIS AND BIOLOGICAL ACTIVITY

Gozyo Sakata* and Kenzi Makino*
Central Research Institute, Nissan Chemical Industries, Ltd.,
Tsuboi-cho, Funabashi, Chiba 274, Japan

Yoshihisa Kurasawa*
School of Pharmaceutical Sciences, Kitasato University,
Shirokane, Minato-ku, Tokyo 108, Japan

Abstract —— This review describes the synthesis and screening data of quinoxaline derivatives mainly reported in the last few years.

This review involves the following contents.

fungal Agent

VII. Successful Development of A New Herbicide Quizalofop-Et

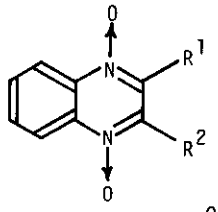
1. Synthesis of Quizalofop-Et and Related Compounds

2. Synthesis of Fluorinated Quizalofop-Et and Related Compounds

I. INTRODUCTION

Numerous quinoxaline derivatives have been synthesized up to date, and many biologically active quinoxaline derivatives have been reported in the journal and patent literatures. For example, quinoxaline 1,4-dioxides 1a,[1] 1b (Carbadox),[2] 1c,[3] and 1d[3] have antibacterial activity, and quinoxaline-2,3-dithione cyclic dithiocarbonate 2a (Morestan)[4] and trithiocarbonate 2b (Eradox)[4] possess fungicidal and insecticidal effects (Chart 1). Quinoxalinyl phosphorothioates 3a (Quinalphos),[5] 3b,[6] and 3c[6] have been evaluated as insecticidal and anthelmintic agents, and 2,3,7-trichloro-6-methylsulfamoylquinoxaline 4[7] has been patented as anticancer agent. 2-Phenyl-3-piperidinoquinoxaline 5 and some of its derivatives[8] are selective herbicides, and quinoxalin-2-ones 6[9] and 7[10] have been shown to have antiinflammatory,[9] tranquilizing,[10] and antidepressant[10] properties. 6-Chloro-2,3-bis(chloromethyl)-quinoxaline 8 has been patented as foliar fungicide.[11,12] Caroverine 9[13] and Quinacilline 10[14] are used as antibacterial agents. Besides the above compounds 1-10, many other biologically active quinoxalines have been reported so far,[15] although these compounds can not be displayed herein because of space limitations. Thus, the cooperative works by the synthetic and screening research groups have continuously been carried out to create various biologically active quinoxalines, and thousands of new quinoxaline derivatives have been produced in a past decade. Recently, a successful development of Quizalofop-Et 11[16] has been reported by a research group of Nissan Chemical Industries, Ltd., which patents it as a potent and selective herbicide.

Hitherto, there have been several reviews[15,17-20] dealing with the quinoxaline chemistry, but the reviews handling both the synthesis and biological activity of quinoxalines have seldom been published. Accordingly, this review describes the

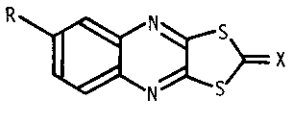


1a R^1=Me, R^2=CH=N(→O)-Me

1b R^1=H, R^2=CH=NNHCOOMe

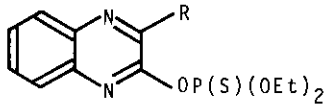
1c R^1=Me, R^2=CH_2OH

1d R^1=R^2=CH_2OH



2a R=Me, X=O

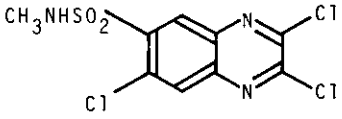
2b R=H, X=S



3a R=H

3b R=OMe

3c R=OEt



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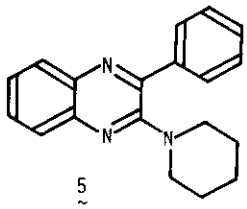

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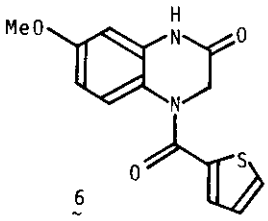

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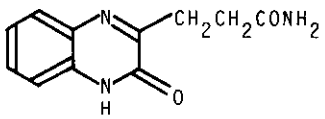

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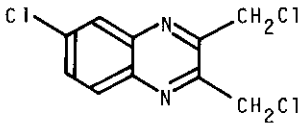

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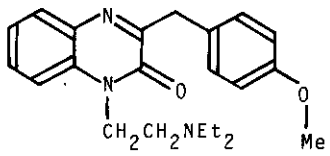

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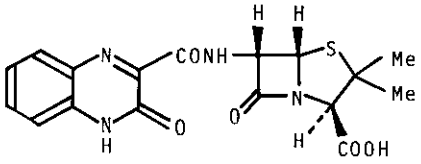

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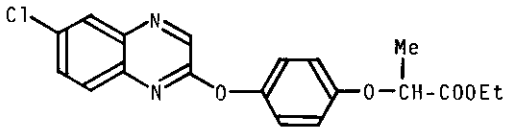

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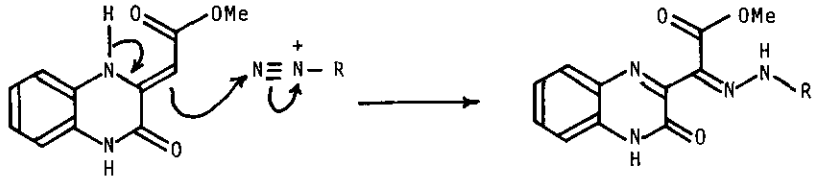
Chart 1

synthesis and screening data of quinoxaline derivatives. Regretfully, the quinoxaline derivatives without the description of the biological activity were omitted in this review. Regrettably, moreover, this review was occupied by our works, leaving no space to incorporate the works by other investigators because of space limitations.

II. SYNTHESIS OF QUINOXALINES UTILIZING ARYL DIAZONIUM SALTS

The methylenic carbon of the ester 12 has been known to react with various electrophilic reagents such as the Vilsmeier reagent, nitrite, acetylenic compound, carbon disulfide, etc.[19] These results suggest that its methylenic carbon would also react with diazonium salts as shown below to give the substituted hydrazones 13, which would be derivatized to various quinoxalines. This section starts from this reaction.



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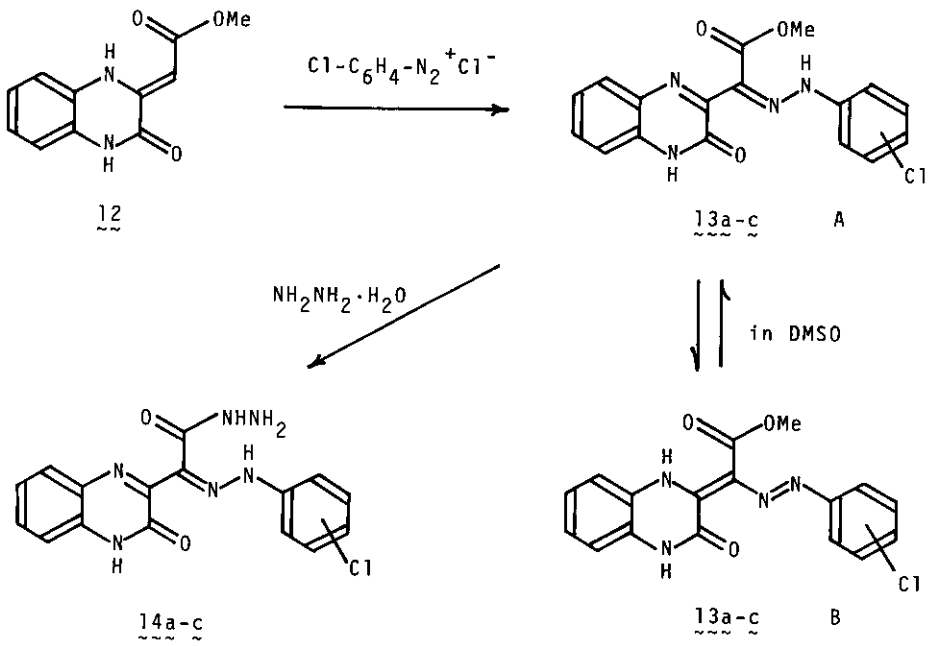
1. 3-(α-ARYLHYDRAZONO)HETEROARYLMETHYL-2-OXO-1,2-DIHYDROQUINOXALINES AND 1-ARYL-3-QUINOXALINYL-1,2,4-TRIAZOL-5-ONES

The reactions of the ester 12 with aryl diazonium chlorides resulted in the methylenic C-diazotization to give the α-arylhydrazonoesters 13a-c (Scheme 1),[21] whose ^{1}H- and ^{13}C-NMR spectral data in DMSO-d_6 provided the evidences for the presence of two tautomers, namely, hydrazone imine form A and diazenyl enamine form B (Scheme 2).[22] The reactions of 13a-c with hydrazine hydrate afforded the α-arylhydrazonohydrazides 14a-c.[21]

The reactions of 14a-c with triethyl orthoesters (*R*=H,Me) produced 3-(α-*arylhydra*-



12

13a-c A

14a-c

13a-c B

a series, o-Cl
b series, m-Cl
c series, p-Cl

Scheme 1

A

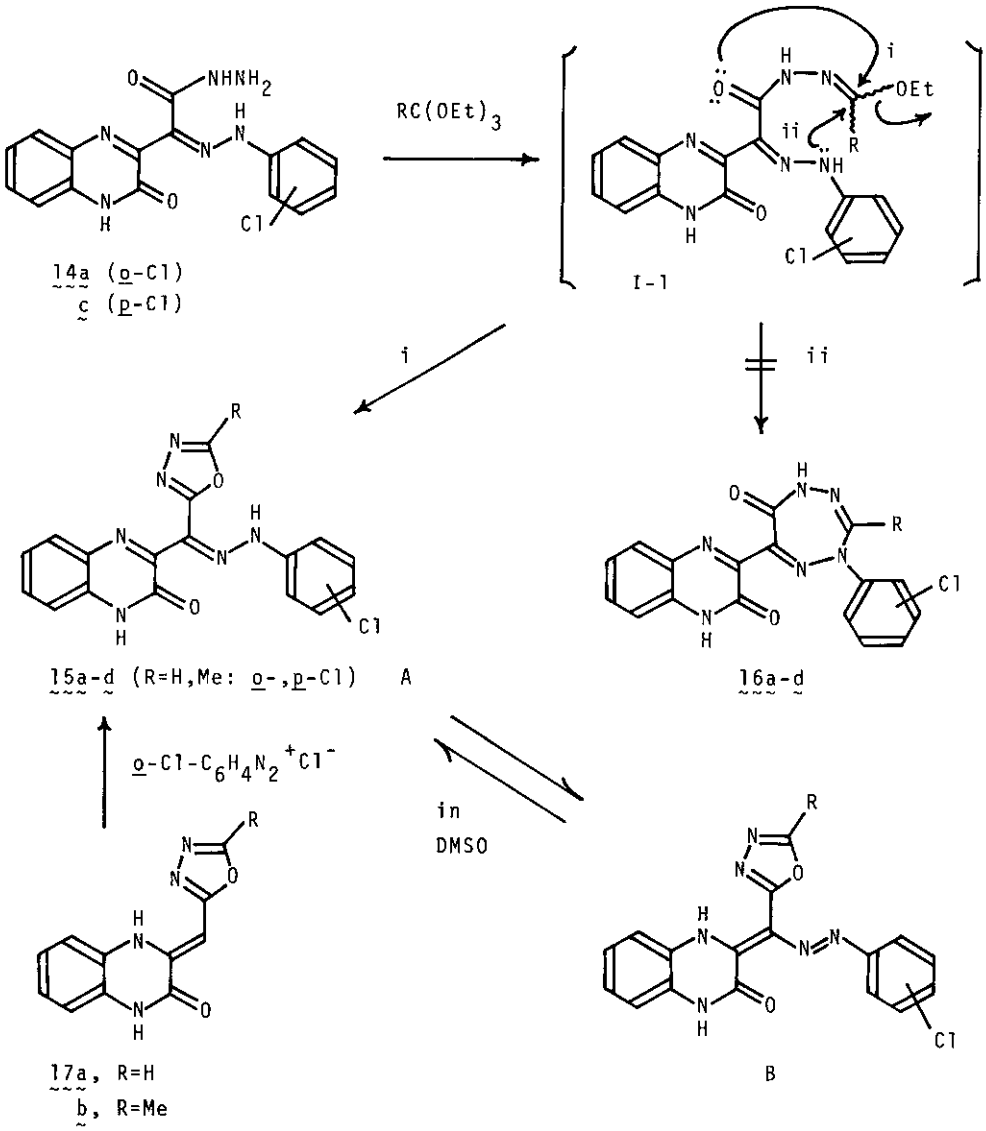
hydrazone imine form

B

diazenyl enamine form

Scheme 2

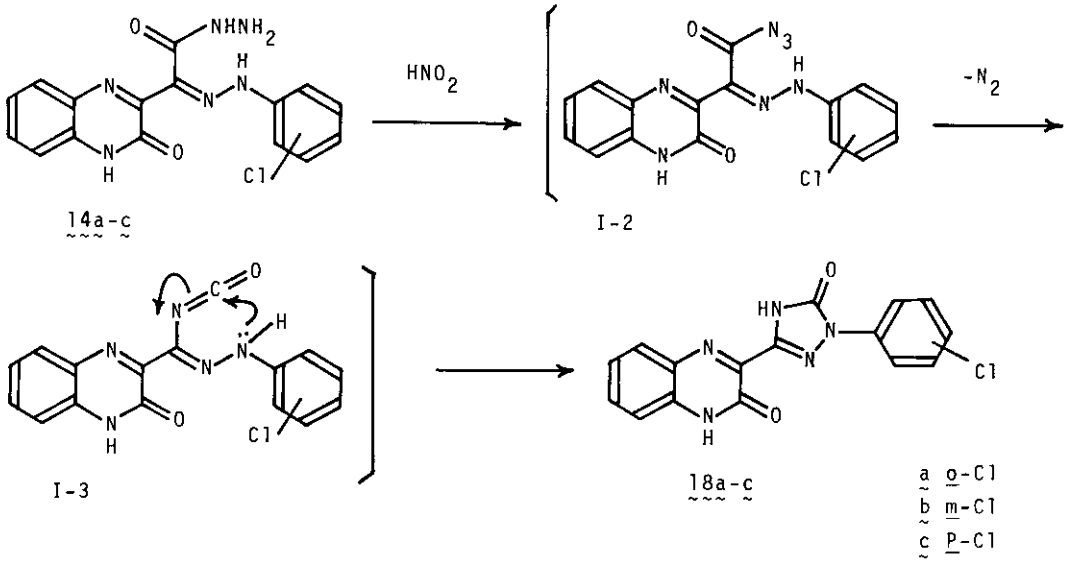
zono-1,3,4-oxadiazol-2-ylmethyl)-2-oxo-1,2-dihydroquinoxalines 15a-d, but not the tetrazepines 16a-d, via possible intermediates I-1 (Scheme 3).[23,24] This cyclization mode was ascertained by the alternate synthesis of 15a,c from compounds 17a and 17b.[25] The ^{1}H- and ^{13}C-nmr spectral data of 15a-d in DMSO-d_6 also supported the tautomeric equilibria between the hydrazone imine form A and the diazenyl en-



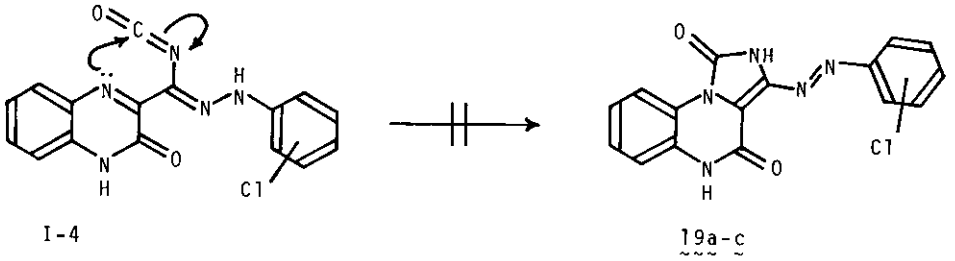
Scheme 3

amine form B.[22]

The reactions of α-arylhydrazonohydrazides 14a-c with nitrous acid effected the Curtius rearrangement to furnish the 1-aryl-3-quinoxalinyl-1,2,4-triazol-5-ones 18a-c (Scheme 4), but not the imidazo[1,2-a]quinoxalines 19a-c (Scheme 5), via intermediates I-2,3.[21]

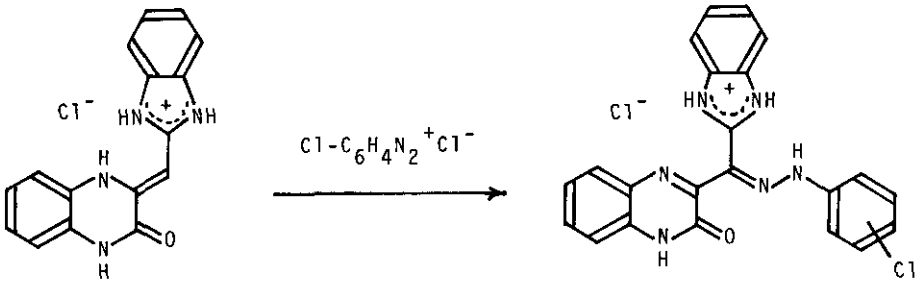


Scheme 4



Scheme 5

3-(α-Arylhydrazonobenzimidazol-2-ylmethyl)-2-oxo-1,2-dihydroquinoxalines 21a-c were also synthesized from compound 20 (Scheme 6).[24]



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21a, o-Cl
b, m-Cl
c, p-Cl

Scheme 6

BIOLOGICAL ACTIVITY

Compounds 15a-d showed the weak antifungal activity (14-33% growth inhibition) against Pythium debaryanum, Pyricularia oryzae, and Rhizoctonia solani at the concentration of 100 ppm, while 15b,d (p-Cl) exhibited the antibacterial activity (100% growth inhibition) against Xanthomonas oryzae at 100 ppm (Table 1). Compounds 21a-c represented the antifungal activity (68-88% growth inhibition) against Pythium debaryanum at 100 ppm, whereas they showed the weak antifungal activity (6-36% growth inhibition) against Pyricularia oryzae and Rhizoctonia solani at 50 and 100 ppm.

2. 1-ARYL-1H-PYRAZOLO[3,4-b]QUINOXALINES

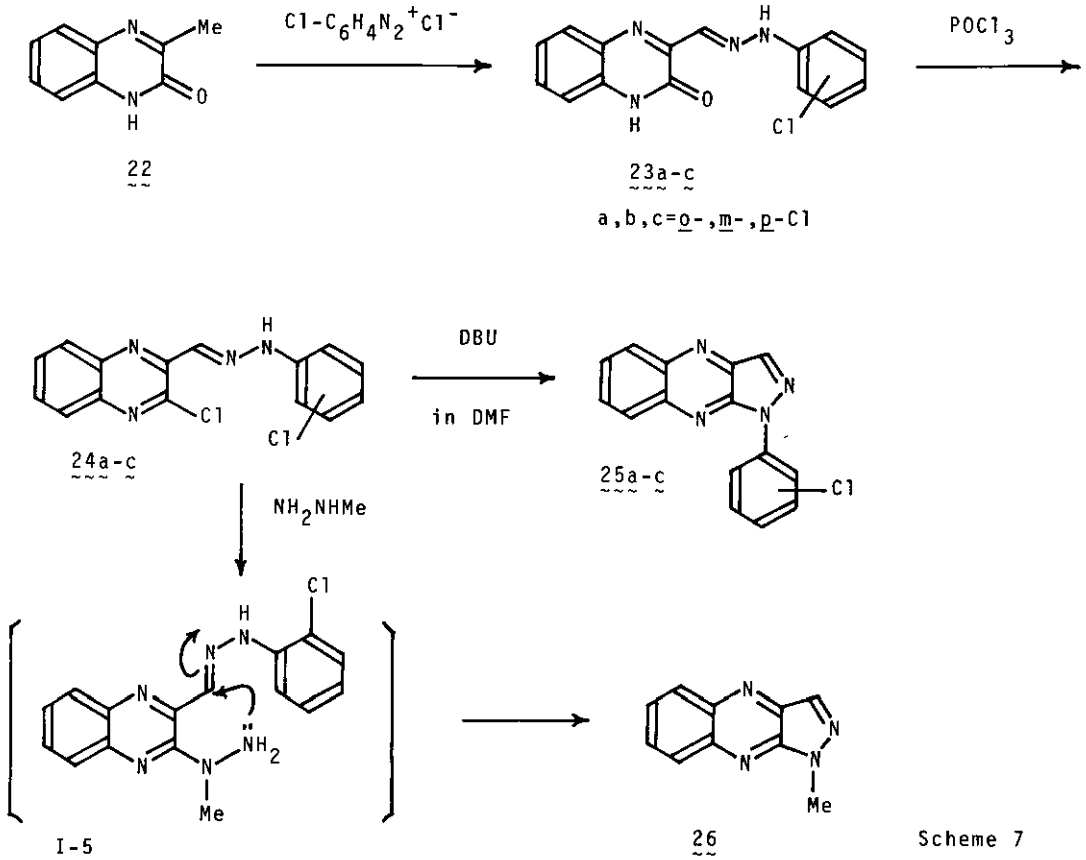
The reactions of 3-methyl-2-oxo-1,2-dihydroquinoxaline 22 with aryl diazonium chlorides also resulted in the diazotization to give the arylhydrazones 23a-c,[26-28] whose chlorinations with $POCl_3$ afforded the 2-chloro derivatives 24a-c. Refluxing of

Table 1. Antifungal and Antibacterial Activities of 15a-d and 21a-c.

Compound	Concentration (ppm)	Activity[a] P.d.	P.o.	R.s.	X.o.[b]
15a	100	14	29	27	
b	100	21	2	24	100
c	100	30	62	27	
d	100	19	28	33	100
21a	100	68	22	67	
	50	46	21	6	
b	100	78	24	27	
	50	50	23	16	
c	100	88	35	36	
	50	49	29	10	

a Growth inhibition (%)

b P.d. — Pythium debaryanum (fungi) P.o. — Pyricularia oryzae (fungi)
R.s. — Rhizoctonia solani (fungi) X.o. — Xanthomonas oryzae (bacteria)



Scheme 7

24a-c and 1,8-diazabicyclo[5,4,0]-7-undecene (DBU) in DMF effected the cyclization to provide 1-aryl-1H-pyrazolo[3,4-b]quinoxalines 25a-c. The reaction of 24a with methylhydrazine produced 1-methyl-1H-pyrazolo[3,4-b]quinoxaline 26[28] (Scheme 7).

BIOLOGICAL ACTIVITY

Compounds 23c and 25a showed the antifungal activity (100% and 96% growth inhibition) against Pythium debaryanum at 100 ppm (Table 2).[28] Compound 25a also exhibited the bactericidal activity (100% growth inhibition) against Xanthomonas oryzae at 100 ppm.[28] The weak antifungal activity was observed against Pyricularia oryzae and Rhizoctonia solani.

Table 2. Antifungal Activity of 23a-c and 25a-c.

Compound	Concentration (ppm)	Activity[a] P.d.	P.o.	R.s.[b]
23a	100	37	7	48
b	100	35	9	45
c	100	100	10	56
25a	100	96	59	79
b	100	58	9	31
c	100	58	10	15

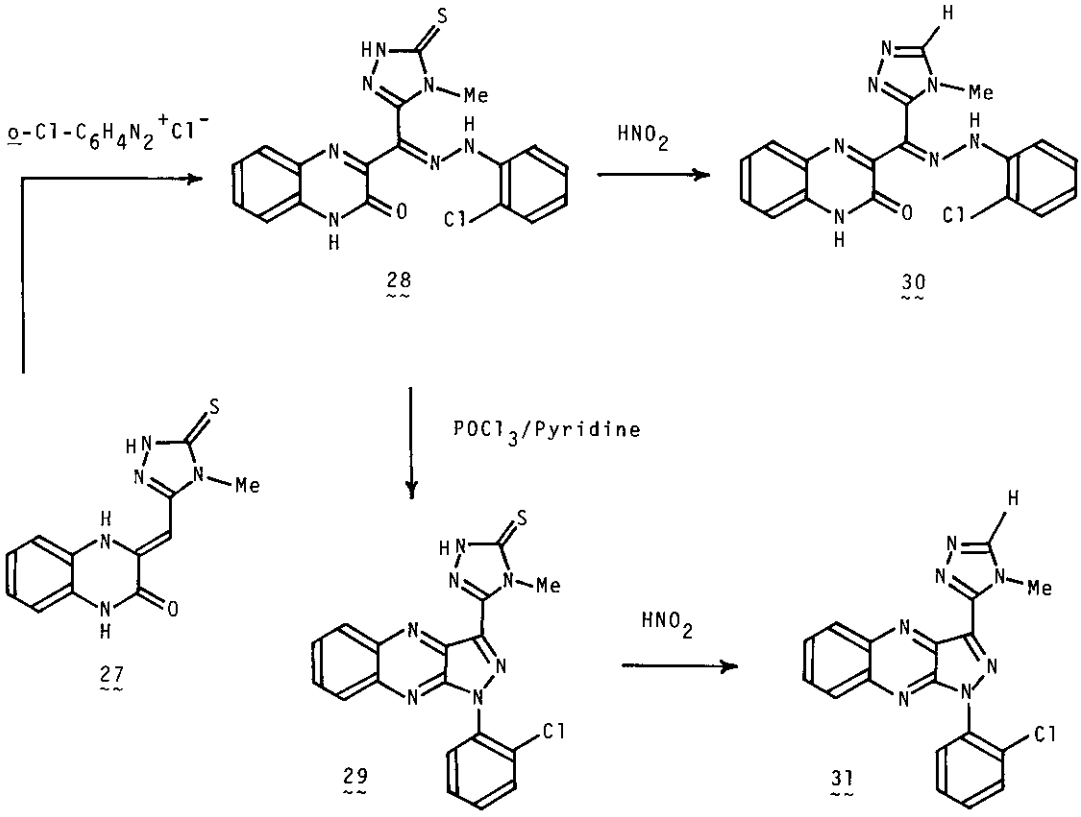
a Growth inhibition (%)

b P.d.— Pythium debaryanum P.o.— Pyricularia oryzae
R.s.— Rhizoctonia solani

3. 1-ARYL-3-HETEROARYL-1H-PYRAZOLO[3,4-b]QUINOXALINES

The reaction of the 3-triazolylmethylenequinoxaline 27 with o-chlorobenzenediazonium chloride gave the hydrazone 28, whose refluxing in $POCl_3$/pyridine resulted in dehydrative cyclization to afford the 1-aryl-3-(triazol-3-yl)pyrazolo[3,4-b]quinoxaline 29.[28,29] The reactions of 28 and 29 with nitrous acid effected sulfur extrusion to produce the hydrazone 30 and 1-aryl-3-(triazol-3-yl)pyrazolo[3,4-b]quino-

xaline 31, respectively (Scheme 8).



Scheme 8

Table 3. Antifungal Activity of 28-31.

Compound	Concentration (ppm)	Activity[a] P.d.	P.o.	R.s.[b]
28	100	47	34	27
29	100	62	42	51
30	100	65	35	46
31	100	70	48	47

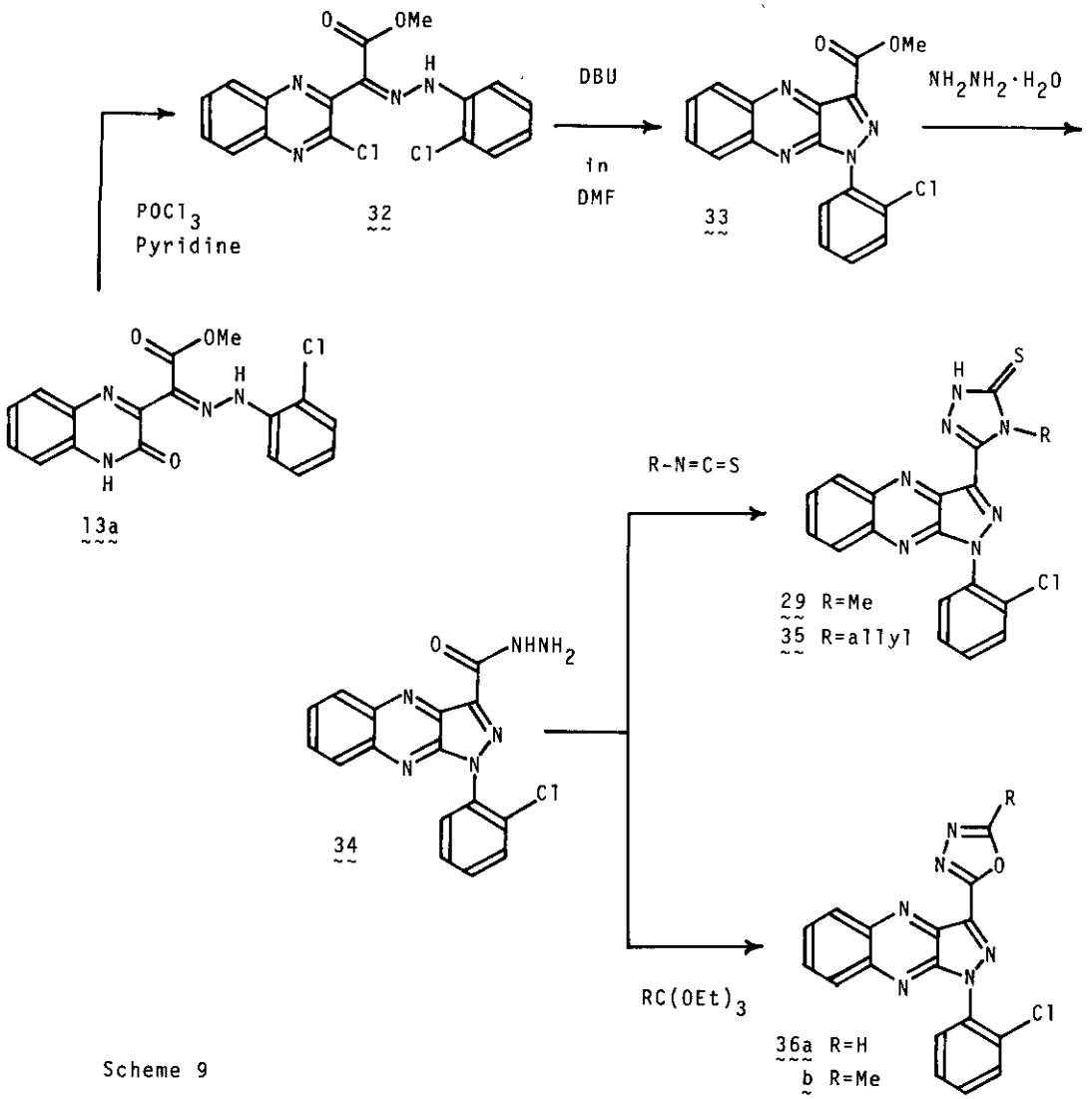
a Growth inhibition (%)

b P.d.— Pythium debaryanum P.o.— Pyricularia oryzae
R.s.— Rhizoctonia solani

BIOLOGICAL ACTIVITY

Compounds 28-31 showed the weak antifungal activity against Pythium debaryanum, Pyricularia oryzae, and Rhizoctonia solani, as shown in Table 3.[28]

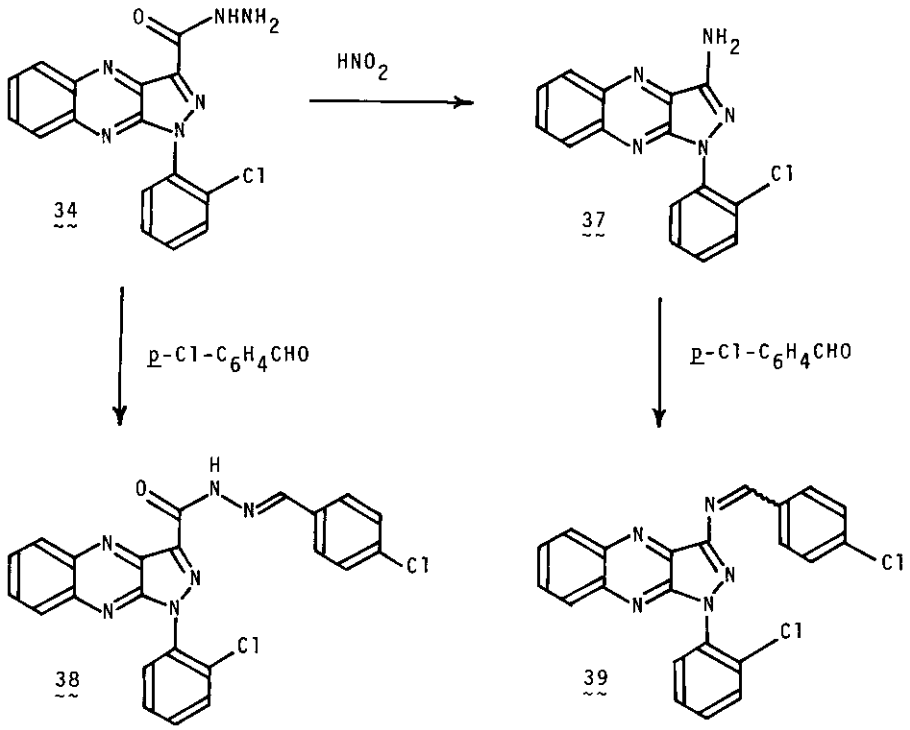
Compound 13a (shown in Scheme 1) is also a good intermediate to 1-aryl-3-heteroarylpyrazolo[3,4-b]quinoxalines 29, 35, and 36a,b (Scheme 9).[30,31] Chlorination



Scheme 9

of 13a with $POCl_3$/pyridine produced the 2-chloro derivative 32, whose refluxing with DBU in DMF resulted in cyclization to give the 1-aryl-3-methoxycarbonylpyrazolo[3,4-b]quinoxaline 33. The reaction of 33 with hydrazine hydrate afforded the 3-hydrazinocarbonyl derivative 34, whose reactions with isothiocyanates and orthoesters in the presence of DBU provided 1-aryl-3-(triazol-3-yl)pyrazolo[3,4-b]quinoxalines 29,35 and 1-aryl-3-(oxadiazol-2-yl)pyrazolo[3,4-b]quinoxalines 36a,b, respectively.

The reaction of 34 with nitrous acid furnished the 3-amino derivative 37 (Scheme 10).[31] The reactions of 34 and 37 with p-chlorobenzaldehyde produced the hydrazone 38 and p-chlorophenylmethyleneamino derivative 39, respectively.



Scheme 10

BIOLOGICAL ACTIVITY

Compounds 33-36 showed the antifungal activity (73-89% growth inhibition) against Pythium debaryanum at 100 ppm, while 32-39 represented the weak antifungal activity against Pyricularia oryzae and Rhizoctonia solani (Table 4).[31]

Table 4. Antifungal Activity of 32-39.

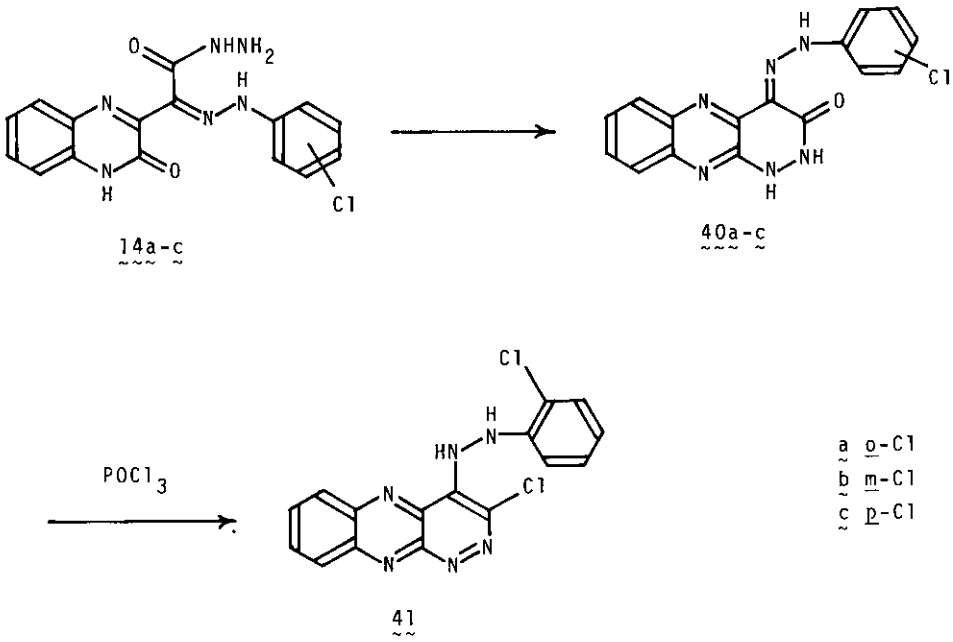
Compound	Concentration (ppm)	Activity[a] P.d.	P.o.	R.s.[b]
32	100	58	42	10
	50	32	34	5
33	100	76	26	10
	50	46	17	8
34	100	80	47	47
	50	65	42	43
35	100	89	56	69
	50	60	55	48
36a	100	80	48	29
	50	24	40	12
36b	100	73	53	50
	50	62	55	34
37	100	43	45	62
	50	22	32	46
38	100	48	22	36
	50	20	4	38
39	100	61	11	26
	50	37	17	16

a Growth inhibition (%)

b P.d.— Pythium debaryanum P.o.— Pyricularia oryzae
R.s.— Rhizoctonia solani

4. PYRIDAZINO[3,4-b]QUINOXALINES

Compounds 14a-c (shown in Section II-1) were also led to pyridazino[3,4-b]quinoxalines 40a-c (Scheme 11).[32] Refluxing of 14a-c and hydrazine dihydrochloride



Scheme 11

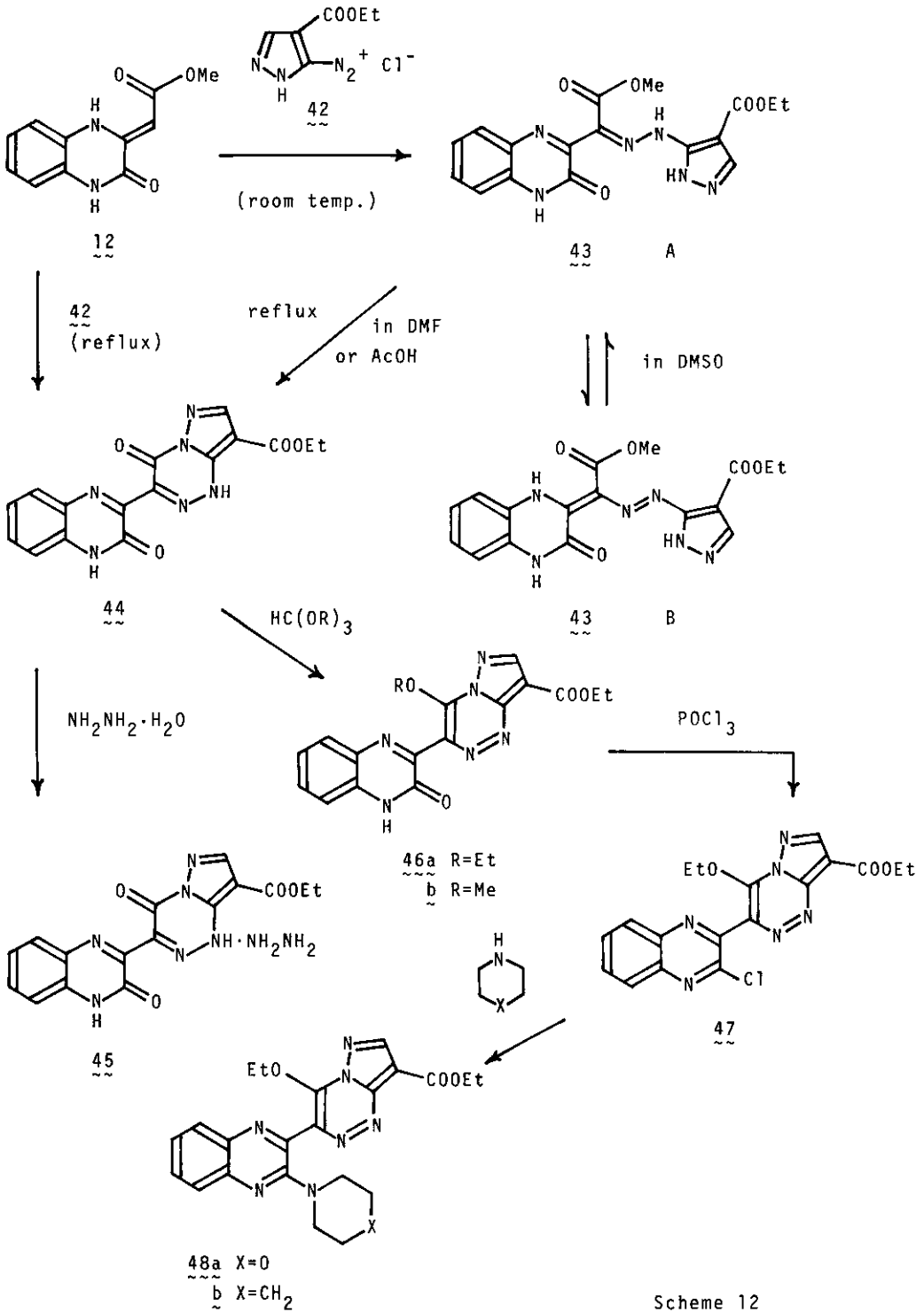
in AcOH resulted in dehydrative cyclization to give 40a-c, and chlorination of 40a with $POCl_3$ provided 3-chloro-4-(o-chlorophenyl)hydrazinopyridazino[3,4-b]quinoxaline 41.

BIOLOGICAL ACTIVITY

Compounds 40a-c and 41 showed no antifungal activity against Pythium debaryanum, Pyricularia oryzae, and Rhizoctonia solani at 100 ppm.

5. 3-QUINOXALINYLPYRAZOLO[5,1-c][1,2,4]TRIAZINES

The reaction of the ester 12 with the pyrazole-5-diazonium chloride 42 gave the pyrazolylhydrazone 43, whose ^{1}H-nmr spectrum in DMSO-d_6 supported the presence of two tautomers 43A and 43B (22:3 or 3:22) (Scheme 12).[33] Refluxing of 43 in DMF or AcOH resulted in cyclization to afford the 3-quinoxalinylpyrazolo[5,1-c][1,2,4]-


COOEt
OMe
42
(room temp.)
12
43 A
42 (reflux)
reflux in DMF or AcOH
in DMSO
44
43 B
HC(OR)3
NH2NH2·H2O
POCl3
46a R=Et
b R=Me
45
47
48a X=O
b X=CH2

Scheme 12

triazine 44, which was also obtained directly from the reaction of the ester 12 with the diazonium salt 42. The reaction of 44 with hydrazine hydrate provided the hydrazinium salt 45, while the reactions of 44 with triethyl and trimethyl orthoformates furnished the ethoxyl 46a and methoxyl 46b derivatives, respectively. The chlorination of 46a with $POCl_3$ gave the 3'-chloro derivative 47, whose reactions with morpholine and piperidine produced the 3'-morpholino 48a and 3'-piperidino 48b[34] derivatives, respectively.

BIOLOGICAL ACTIVITY

Compounds 44-47 showed the weak antifungal activity (28-45% growth inhibition) against Pythium debaryanum at 100 ppm.[35]

III. SYNTHESIS OF 3-QUINOXALINYL-1,2,4-TRIAZOLO[3,4-f][1,2,4]TRIAZINES

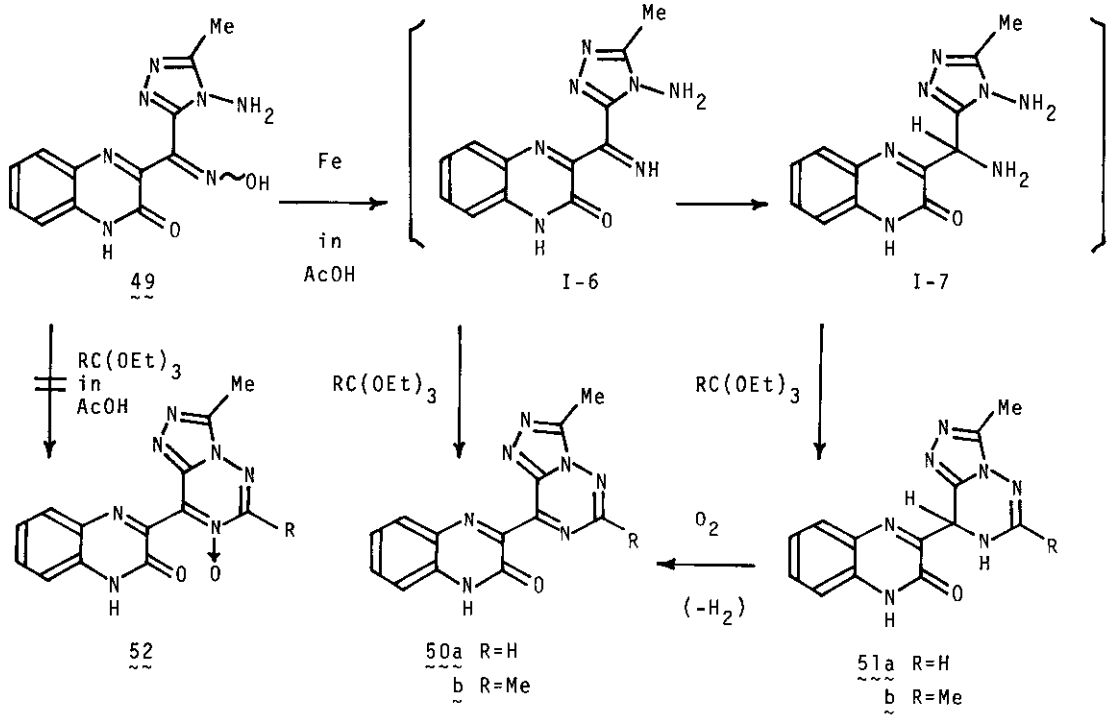
There are many biologically active compounds among 1,2,4-triazole derivatives.[19] This section describes the preparation and screening data of the condensed 1,2,4-triazoles 50a,b (Scheme 13).[36,37]
The reactions of the oxime 49[38] with orthoesters (R=H,Me) and Fe powder in acetic acid resulted in reduction and cyclization to give the 3-quinoxalinyl-1,2,4-triazolo[3,4-f][1,2,4]triazines 50a,b and the dihydro compounds 51a,b, presumably via intermediates I-6 and I-7, respectively. The dihydro compounds 51a,b are susceptible to oxidation, changing into 50a,b, respectively. The absence of Fe powder in the above reactions did not afford the N-oxides 52, but recovered the starting material 49.

BIOLOGICAL ACTIVITY

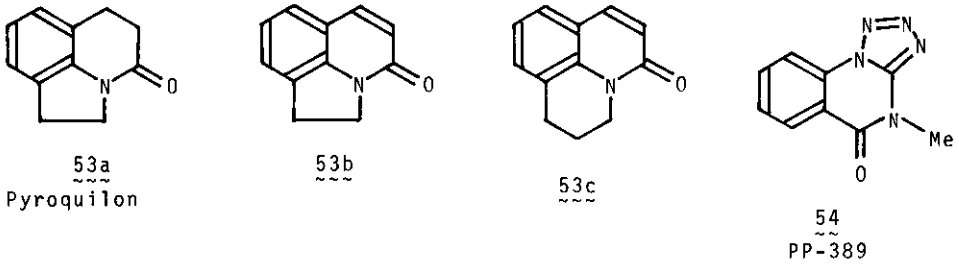
Compounds 50 showed no antifungal and antibacterial activities against the microorganisms described in the foregoing sections.[39]

VI. SYNTHESIS OF QUINOXALINES AIMING AT MELANINE BIOSYNTHESIS INHIBITOR

The pyrrolo[3,2,1-i,j]quinolinone 53a (Pyroquilon) and its analogues 53b,c,[40]



Scheme 13



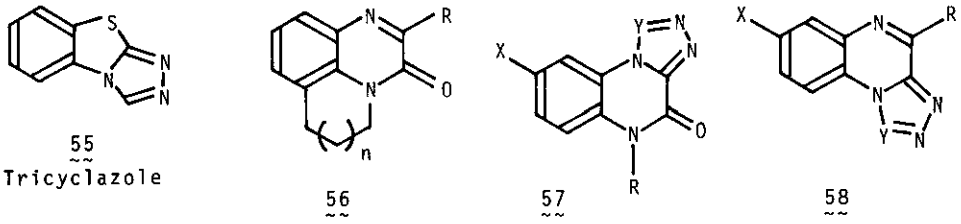
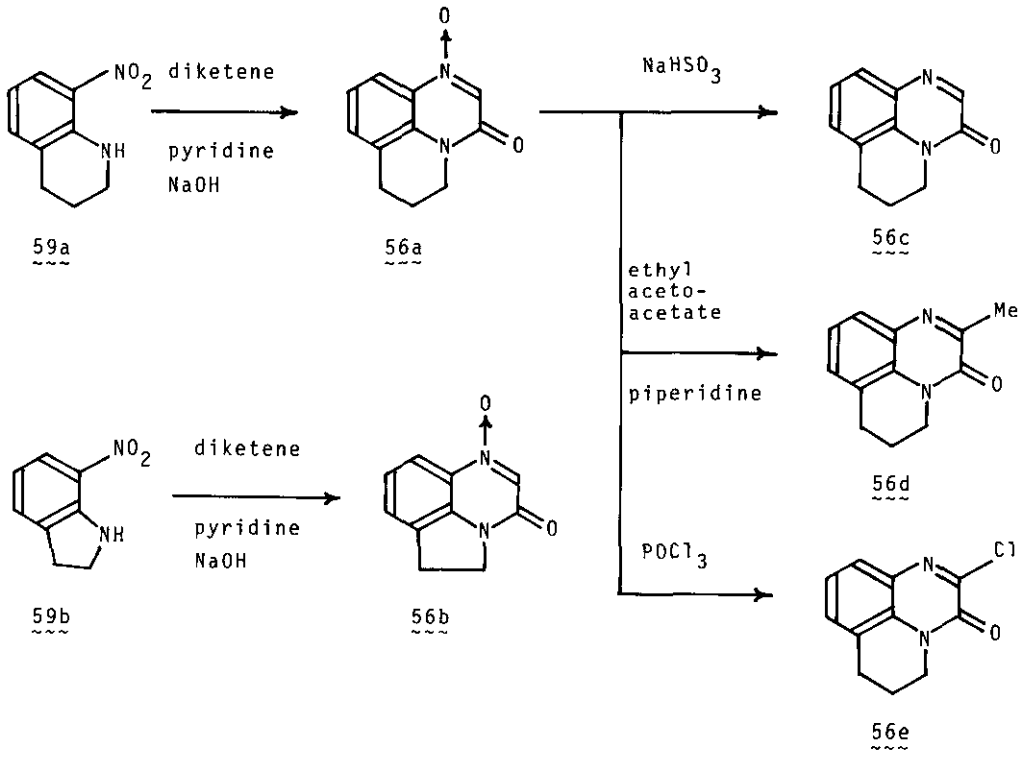


Chart 2

the tetrazolo[1,5-a]quinazolinone 54 (PP-389),[41] and the triazolo[3,4-b]benzothiazole 55 (Tricyclazole)[42] (Chart 2) have been reported to show the excellent fungicidal activity against Pyricularia oryzae, inhibiting the pathway of melanine biosynthesis. The target compounds in this section are the quinoxalines 56-58 structurally analogous to compounds 53-55.

1. PYRIDO[3,2,1-i,j]QUINOXALINES AND PYRROLO[3,2,1-i,j]QUINOXALINES

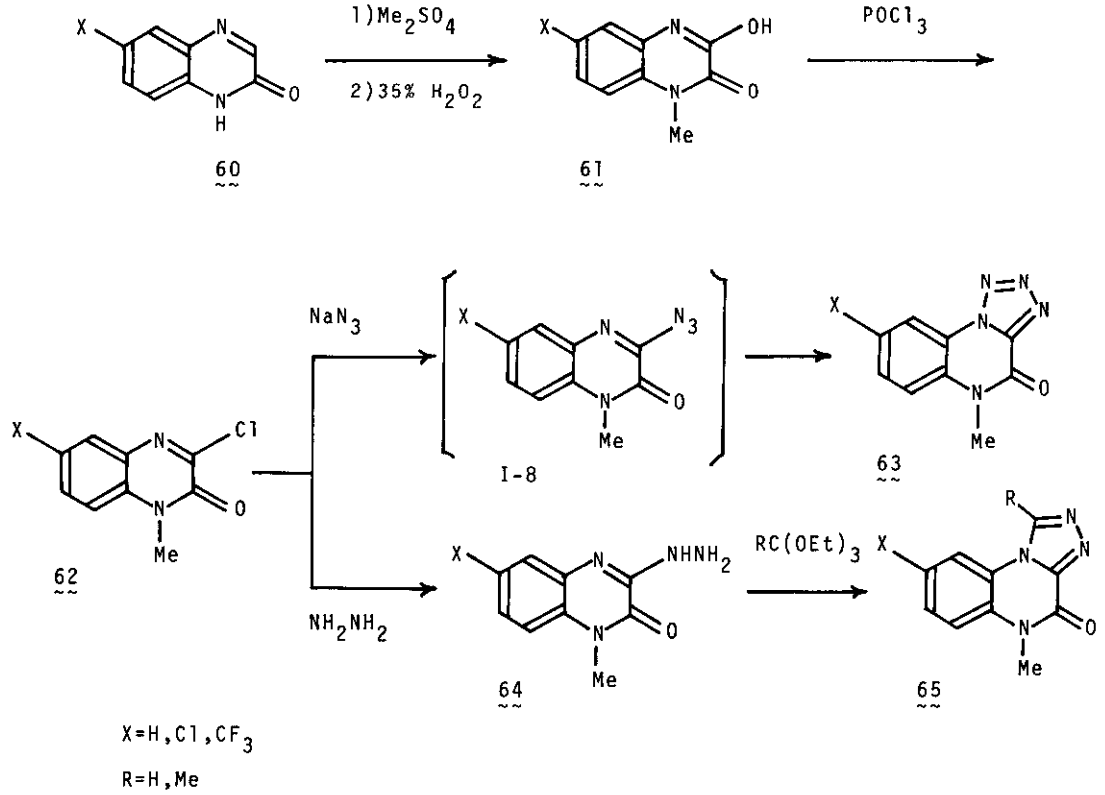
The reaction of the tetrahydroquinoline 59a with diketene and NaOH gave the pyrido-[3,2,1-i,j]quinoxaline 7-oxide 56a, and a similar reaction of the indoline 59b afforded the pyrrolo[3,2,1-i,j]quinoxaline 6-oxide 56b (Scheme 14).[43] The reactions of 56a with $NaHSO_3$, ethyl acetoacetate, and $POCl_3$ provided the requisite quinoxalines 56c-e, respectively. The mechanisms for the above reactions are shown in the original paper in detail.[43]



Scheme 14

2. TETRAZOLO[1,5-a]QUINOXALINES AND TRIAZOLO[4,3-a]QUINOXALINES

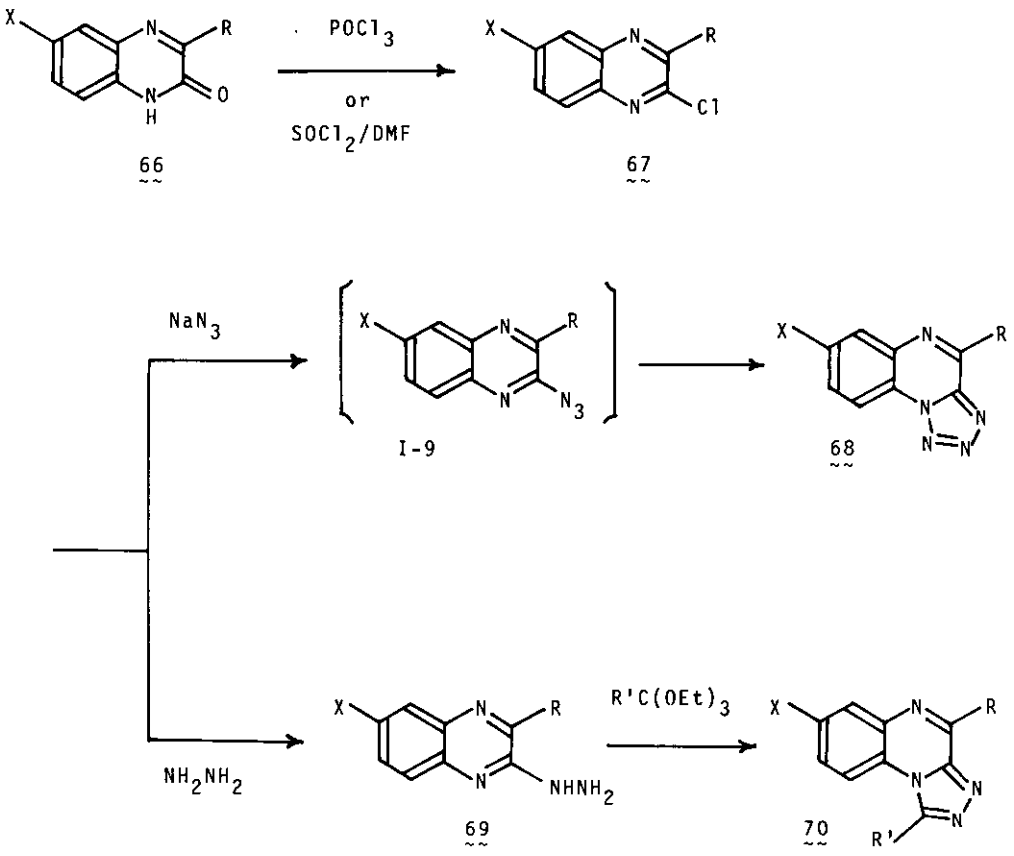
The reactions of the quinoxalinones 60[44] with Me_2SO_4 and then with 35% H_2O_2 gave the 3-hydroxy-1-methyl derivatives 61, whose chlorinations with $POCl_3$ afforded the 3-chloro-1-methyl derivatives 62 (Scheme 15).[45] The reactions of 62 with NaN_3 furnished the tetrazolo[1,5-a]quinoxalines 63 via azide intermediates I-8, while the reactions of 62 with hydrazine hydrate and then with orthoesters provided the triazolo[4,3-a]quinoxalines 65 via the hydrazides 64.



Scheme 15

The chlorinations of the quinoxalinones 66[44,46] with $POCl_3$ or $SOCl_2$/DMF gave the 2-chloro derivatives 67, whose similar reactions to those shown in Scheme 15 afforded the tetrazolo[1,5-a]quinoxalines 68 and the triazolo[4,3-a]quinoxalines 70

via azide intermediates I-9 and the hydrazides 69, respectively (Scheme 16).[45]



X=H,Cl,Br,CF_3
R=H,Me,NH_2
R'=H,Me

Scheme 16

BIOLOGICAL ACTIVITY

Compounds 56a and 56c exhibited the activity inhibiting the melanine biosynthesis as effective as Pyroquilon 53a, and they also represented the fungicidal activity against Pyricularia oryzae (Table 5).[47]

Compounds 65 (X=R=H), 68 (X=Cl, R=H), and 70 (X=Cl, R=H, R'=Me) showed the excellent preventive activity against Plasmodiophora brassicae, Sphaerotheca fuliginea,

and Pyricularia oryzae, respectively.[45]

Table 5. Fungicidal Activity of 56 against Pyricularia oryzae.

Compound	Inhibition of Melanine Biosynthesis				Hyphal Growth Inhibition				Preventive Activity		
	100	10	1	ppm[a]	100	10	1	ppm[a]	100	10	ppm[a]
56a	+	+	-		17	9	7		90	70	
56c	+	+	+		65	4	4		100	80	
53a[b]	+	+	+		17	2	2		100	100	

a Concentration

b Pyroquilon

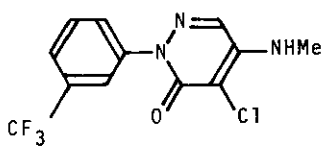
V. SYNTHESIS OF 2-PYRIDAZINYLQUINOXALINES AIMING AT CAROTENOID BIOSYNTHESIS INHIBITOR

Monometflurazone 71 (Scheme 17) and its related compounds have been used as a pre-emergence herbicides,[48] and the chlorine atom of Monometflurazone is known to be essential for the herbicidal activity. This compound has also been known to inhibit the carotenoid biosynthesis. The target compounds in this section are the 2-pyridazinylquinoxalines 74-79 structurally analogous to Monometflurazone.

The reactions of 69a-c with mucochloric acid 72 gave the 2-pyridazinylquinoxalines 74a-c, whose reactions with dimethylamine, methylamine, and MeONa afforded the 5'-substituted derivatives 75a-c, 76a-c, and 77a-c, respectively.[49] The reactions of 69a-c with dichloromaleic anhydride 73 provided the 6'-hydroxyl derivatives 78a-c, whose acetylation furnished the 6'-acetyl derivatives 79a-c.

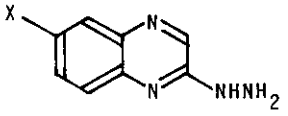
BIOLOGICAL ACTIVITY

2-Pyridazinylquinoxalines 74-79 showed no herbicidal activity, but 76a-c exhibited

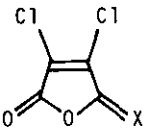


71

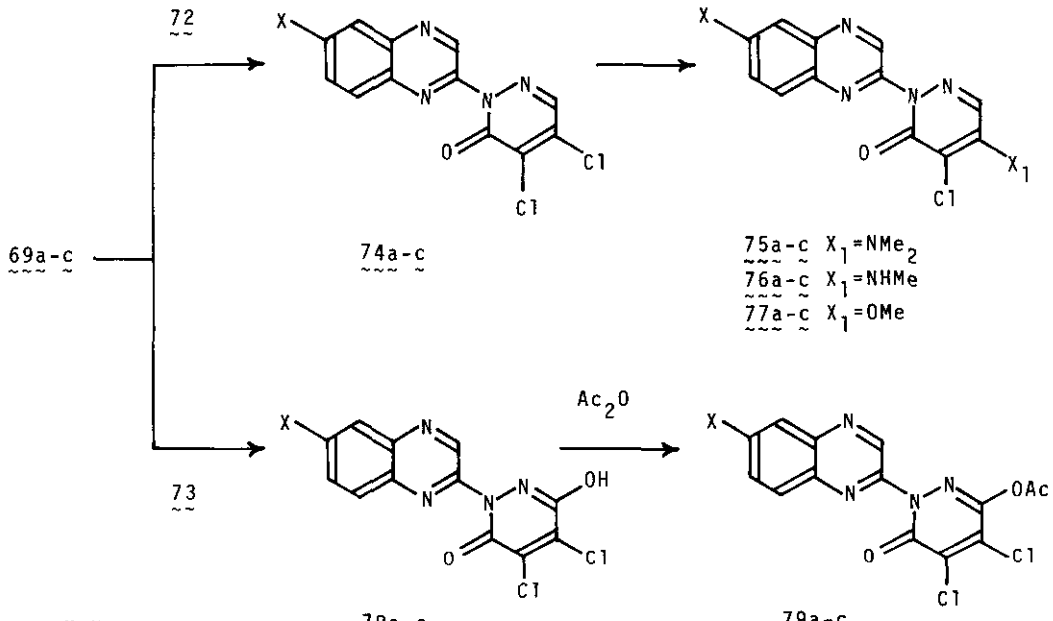
Monometflurazone



69a-c



72 X=H,OH
73 X=O



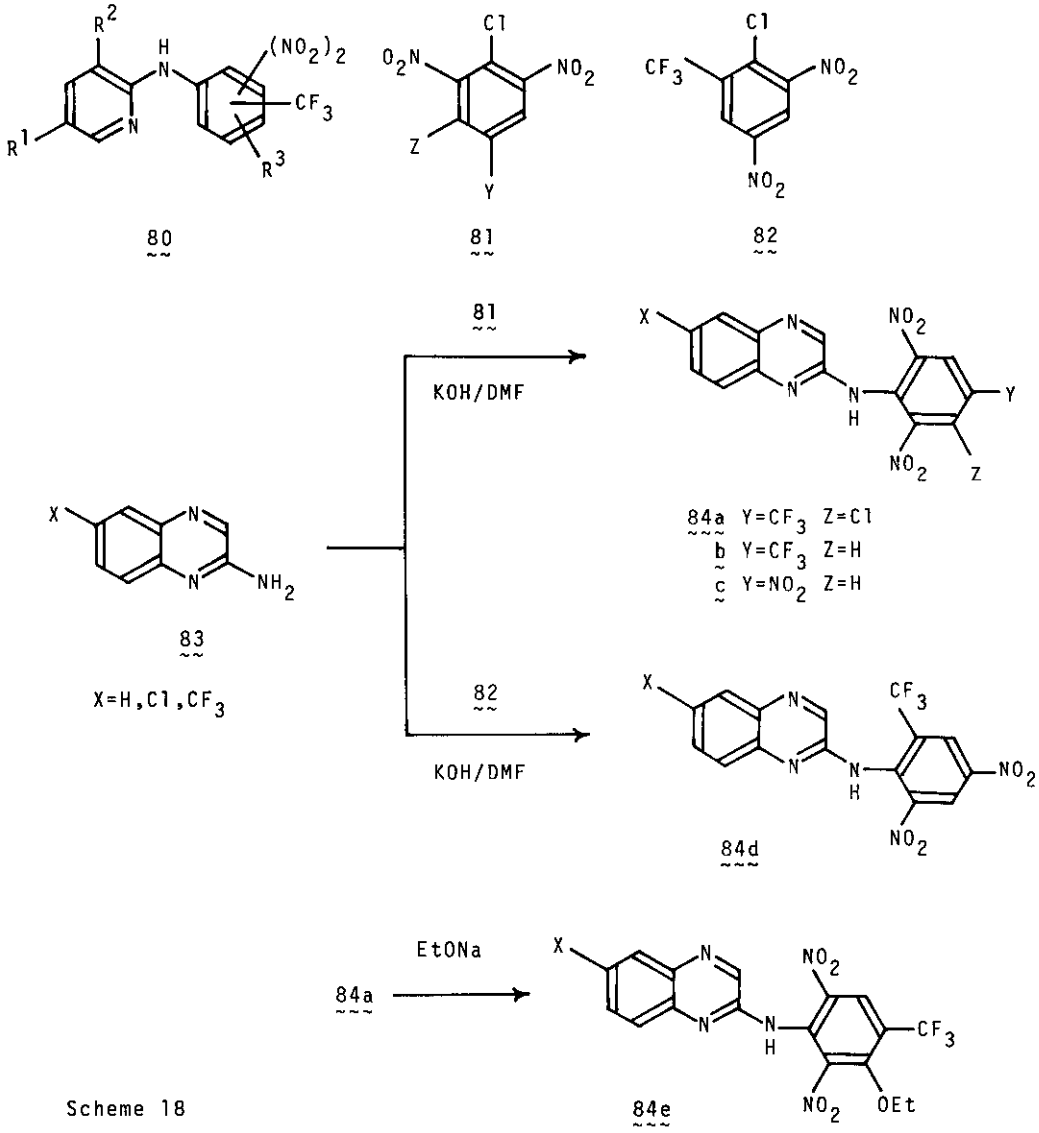
a X=H
b X=Cl
c X=CF_3

Scheme 17

the antifungal activity against Pyricularia oryzae.[50]

VI. SYNTHESIS OF 2-(DINITROTRIFLUOROMETHYLANILINO)QUINOXALINES AIMING AT ANTIFUNGAL AGENT

The 2-(dinitrotrifluoromethylanilino)pyridines 80 (Scheme 18) have been known as



Scheme 18

the potential antifungal agents.[51] The project was carried out to search for more potential fungicidal agents by the substitution of the pyridine ring of 80 with the quinoxaline ring. This section describes the synthesis and screening data of the 2-(dinitrotrifluoromethylanilino)quinoxalines 84a-e[52] structurally analogous to compounds 80.

The reactions of the 2-aminoquinoxalines 83[52] with the dinitrohalobenzenes 81 and 82 gave the requisite 2-(dinitrotrifluoromethylanilino)quinoxalines 84a-d. Treatment of 84a with EtONa afforded the 3'-ethoxyl derivative 84e.

BIOLOGICAL ACTIVITY

Compounds 84a (X=H, Cl, CF_3) showed the excellent hyphal growth inhibitory activity against Pyricularia oryzae, Rhizoctonia solani, and Botrytis cinerea and the preventive activity against rice blast, sheath blight, and downy mildew (Table 6).[53]

Table 6. Fungicidal Activity of 84a.

A. in vitro (Hyphal Growth Inhibition)

Compound	Pyricularia oryzae			Rhizoctonia solani			Botrytis cinerea				
X	5	2.5	0.5	25	5	1	50	10	5	1	ppm[a]
H	100	100	60	100	99	99	—	—	—	—	
Cl	100	100	81	100	100	93	100	90	88	79	
CF_3	100	100	86	100	98	98	90	95	90	81	

B. in vivo (Preventive Activity)

Compound	Rice blast			Sheath blight			Gray mold			Downy mildew		
X	100	50	10	500	100	20	500	100	50	500	100	ppm[a]
H	87	—	—	95	70	40	0	—	—	85	60	
Cl	97	98	80	100	100	60	0	—	—	100	70	
CF_3	87	87	70	90	85	60	0	—	—	95	50	

a Concentration

VII. SUCCESSFUL DEVELOPMENT OF A NEW HERBICIDE QUIZALOFOP-ET

2,4-Dichlorophenoxyacetic acid (2,4-D) 85[54] and 2-(2,4,5-trichlorophenoxy)propanoic acid (2,4,5-TP) 86[55] (Chart 3) known as typical phenoxyfatty acid herbicides have been patented in 1960s, and Diclofop-Me 87 known as phenoxyphenoxyfatty acid herbicide has been developed in 1970s.[56] The substitution of the para position of 2-phenoxypropanoic acid with the halogen or trifluoromethyl group generally realizes the herbicidal activity particularly against broad leaf plants, while the replacement of the same position with the substituted phenoxy or pyridinyloxy group effects the strong grass killer property.[57-59]

In the early 1980s, the heteroaryloxyphenoxypropanoic acid derivatives have been developed as the selective herbicides, and the successful researches have led to the patents of Fluazifop-Bu 88,[60] Fentiaprop-Et,[61] and Fenoxaprop-Et,[62] which possess the pyridinyloxy, benzothiazolyloxy, and benzoxazolyloxy groups, respectively, in their molecules as the heteroaryloxy moiety. These three herbicides were effective for controlling gramineous weeds without any phytotoxicity to broad leaf crop plants as well as broad leaf weeds especially in a post-emergence treatment.

Thus, the above results clarified that the substituted phenoxy or heteroaryloxy group acted an important role for the appearance of the grass killer property.

The research group of Nissan Chemical Industries, Ltd. further studied to search for new compounds with the herbicidal activity. In consideration of the above results, this research group synthesized two series of new compounds 2-(2-naphthoxy)-propanoic acids and 2-[4-(2-quinolyloxy)phenoxy]propanoic acids, and found that several of them showed the strong grass killer activity.[63] Moreover, the research group extended this idea to other condensed heterocycles such as isoquinoline, quinazoline, phthalazine, quinoxaline, and benzotriazine as the heterocyclic moiety. As the result, 2-[4-(2-quinoxalinyloxy)phenoxy]propanoic acid derivatives were found to show the excellent grass killer activity. Especially, Quizalofop-Et 11 exhibited the excellent screening data.[64] This section mainly describes the development and screening data of Quizalofop-Et and its related compounds.

1. SYNTHESIS OF QUIZALOFOP-ET AND ITS RELATED COMPOUNDS

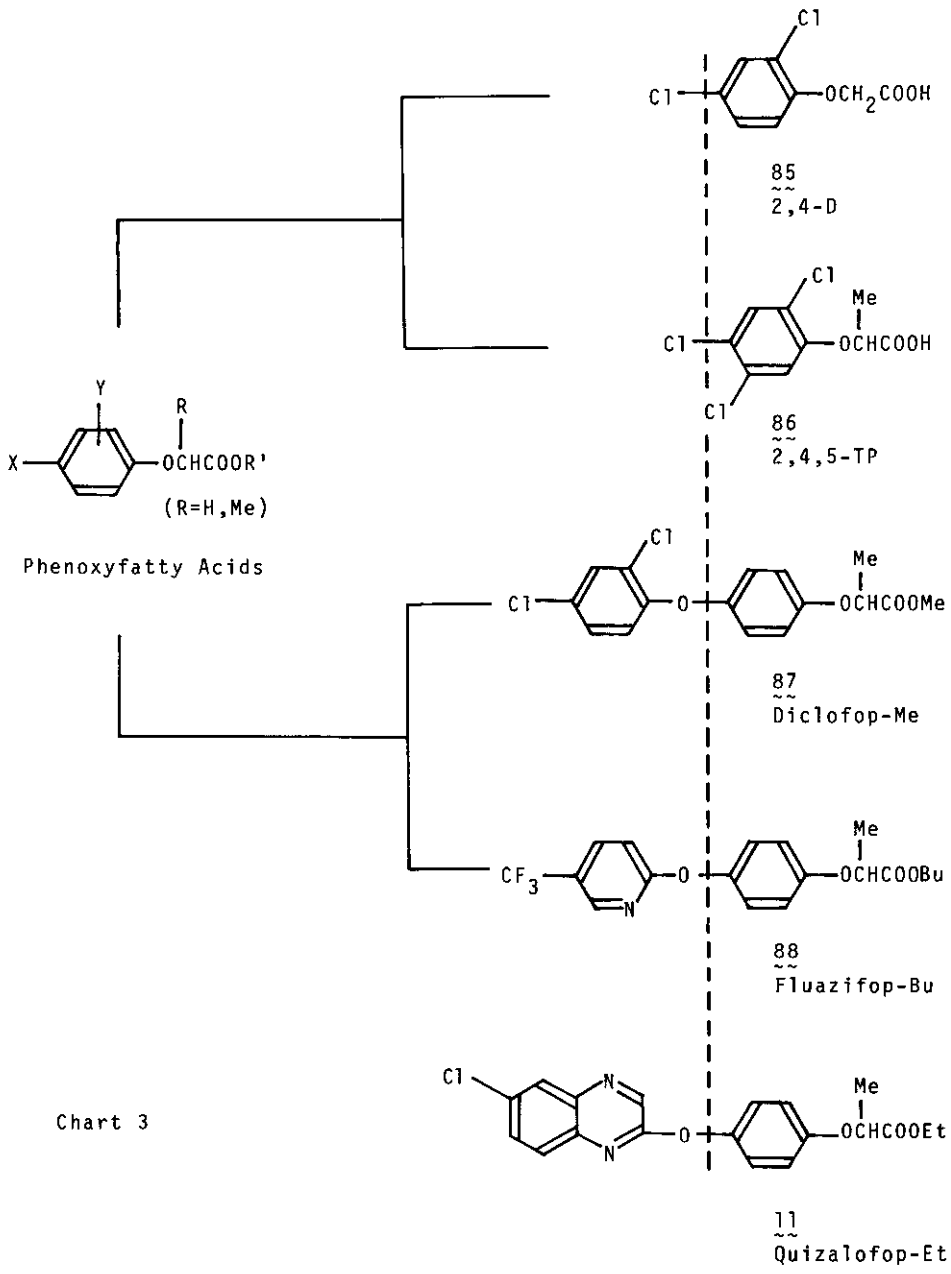
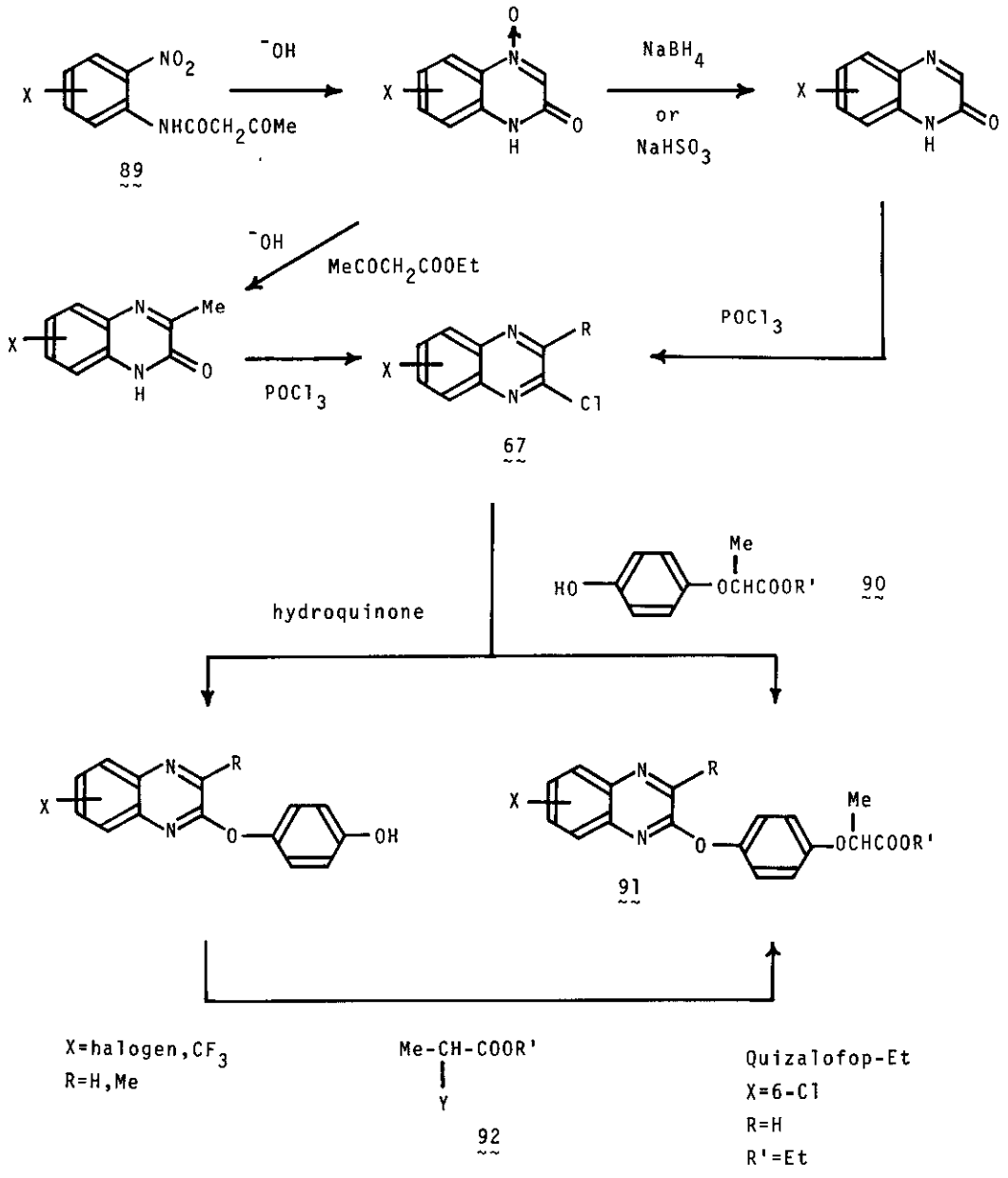


Chart 3

Since the quinoxaline ring was selected as the target heterocyclic moiety, various substituted quinoxalines 67[44,46] were elaborated at first starting from the substituted 2-acylaminonitrobenzenes 89 (Scheme 19).

The reactions of 67 with 2-(4-hydroxyphenoxy)propanoic acid derivatives 90 gave 2-[4-(2-quinoxalinyloxy)phenoxy]propanoic acid derivatives 91, which were also obtained from the reactions of 67 with hydroquinone and then with the 2-halopropanoic acid derivatives 92.[65,66]



Scheme 19

BIOLOGICAL ACTIVITY

When R was chlorine, bromine, or alkyl group in compounds 91, the herbicidal activity was very low. Where R was hydrogen, compounds 91 showed the strong herbicidal activity against gramineous weeds. Moreover, the herbicidal activity was delicately changed due to the kind, number, and position of the substituents X on benzene nucleus of the quinoxaline ring. The structural optimization for the general formula of 91 clarified that the halogen (F, Cl, Br, I) or trifluoromethyl group at the 6-position was most suitable for the herbicidal activity. The other substituents and positions on the benzene nucleus showed only weak or no activity

Table 7. Herbicidal Activity and Crop Selectivity of 91 (R=H).

Compound		Activity (Post)[a]							
X	R'	a	b	c	d	e	f	g	h[b]
H	Me	4	3	3	4	0	0	0	0
5-Cl	Me	0	0	0	0	0	0	0	0
6-Cl	Me	5	5	5	5	0	0	0	0
6-Cl	Et	5	5	5	5	0	0	0	0
7-Cl	Me	3	2	3	3	0	0	0	0
8-Cl	Me	0	0	0	0	0	0	0	0
$6,7\text{-Cl}_2$	Me	5	5	5	5	0	0	0	0
6-F	Me	5	5	5	5	0	0	0	0
6-Br	Me	5	5	5	5	0	0	0	0
6-I	Me	5	4	5	4	0	0	0	0
6-CF_3	Me	5	5	5	5	0	0	0	0
6-Me	Me	2	1	0	0	0	0	0	0
6-NO_2	Me	0	0	0	0	0	0	0	0
6-MeO	Me	1	0	0	0	0	0	0	0
$6\text{-F}_2\text{CHO}$	Et	0	0	0	0	0	0	0	0

a Dose rate of each compound is 1.0 kg a.i./ha. Growth stage of all plants are at the 3-4 leaf stage. Growth inhibition: 5 - 100% kill, zero - no effect.

b a: Echinochloa crus-galli, b: Digitaria sanguinalis, c: Avena fatua, d: Sorghum halepence, e: Glysine max, f: Gossypium spp., g: Beta vulgaris, h: Brassica napus L.

(Table 7). Furthermore, the herbicidal activity of 91 decreased as the lipophilicity of the ester moiety of 91 increased.[67] In this series of compounds, Quizalofop-Et 11 represented the excellent screening and toxicological data. It was also found that the herbicidal activity of Quizalofop-Et was influenced by the chiral center of the propanoic acid moiety, and the (R)-(+)-isomer was found to be most active.[68,69]

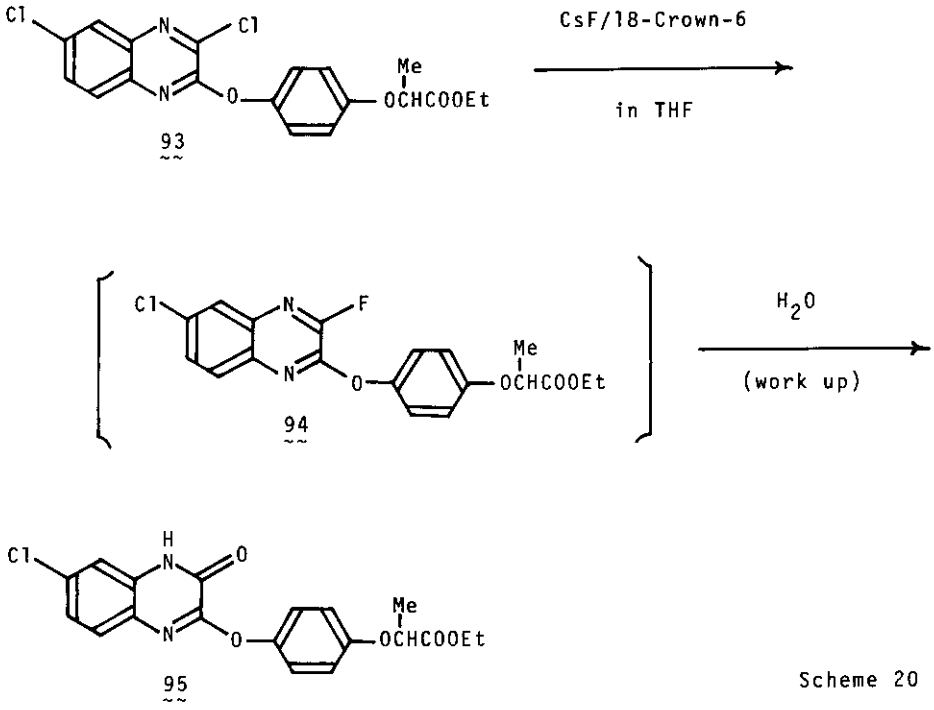
The extensive field trials of Quizalofop-Et covering a wide range of agricultural and climatic conditions have demonstrated its excellent activity against grass weeds in all climatic conditions. The control of annual grasses such as large crabgrass, goosegrass, and fall panicum was achieved at the rate of 0.05-0.15 kg a.i./ha, and johnsongrass was controlled at the rate of 0.11-0.22 kg a.i./ha. The phytotoxicity to soybean was not observed, and its harvest was satisfactory in comparison with the untreated blocks.[65]

2. SYNTHESIS OF FLUORINATED QUIZALOFOP-ET AND ITS RELATED COMPOUNDS

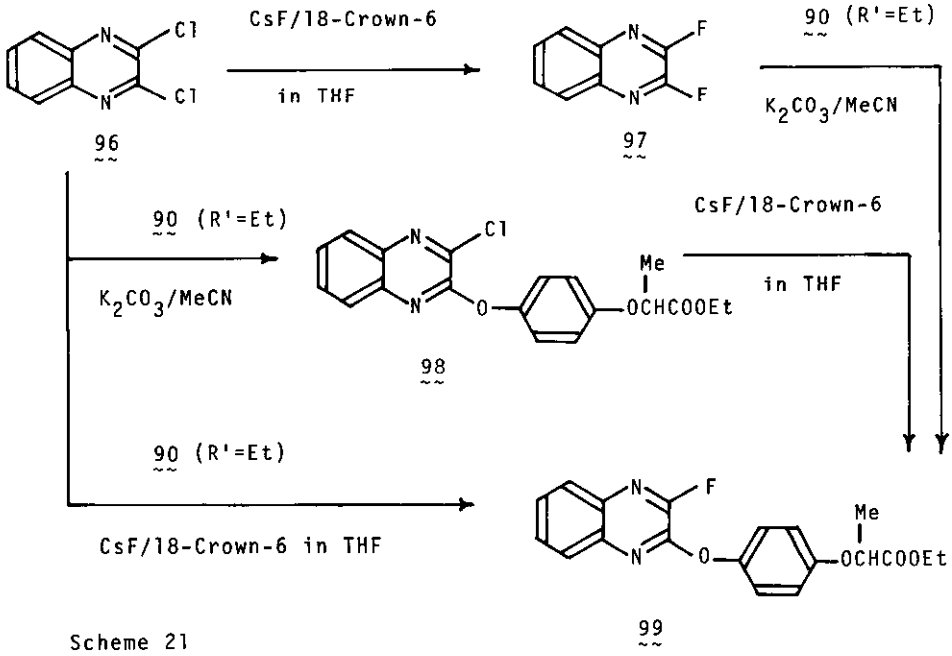
The reaction of the chloro derivative 93 with CsF/18-Crown-6 in THF afforded the fluorinated derivative 94, but this compound was easily hydrolyzed to the oxo derivative 95 during the isolation procedure (Scheme 20).[70] This hydrolysis would be due to the electron-withdrawing property of the 6-chloro atom in the quinoxaline ring. Accordingly, 2,3-dichloroquinoxaline 96 was transformed into ethyl 2-[4-(3-fluoro-2-quinoxalinyloxy)phenoxy]propanoate 99 directly or *via* compounds 97[71] and 98 (Scheme 21).

BIOLOGICAL ACTIVITY

The growth inhibitory activity of 99 to rice plant (*Oryza sativa*) was lower than that of 91 (X=R=H, R'=Et). After all, the herbicidal activity of 2-[4-(2-quinoxalinyloxy)phenoxy]propanoates was found to increase in the decreasing order of bulkiness of the 3-substituent on the quinoxaline ring.[70]



Scheme 20



Scheme 21

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