RECENT PROGRESS IN THE QUINOXALINE CHEMISTRY: UTILITY OF 3-ALKOXYCARBONYLMETHYLENE-2-OXO-1,2,3,4-TETRAHYDROQUINOXALINES AS STARTING MATERIALS

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Abstract —— 3-Alkoxycarbonylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxalines 1 have been converted into various quinoxaline derivatives via versatile intermediates by the facile synthetic methods. This review describes these synthetic routes, including the mechanistic considerations and the spectroscopic properties.

This review involves the following contents.

b. Pyrido[1,2-a]pyrimidylquinoxaline and Pyridazino[3,4-b]quinoxalines

c. Quinoxalinyl-1,5-benzodiazepines and Benzimidazolylmethylenequinoxaline

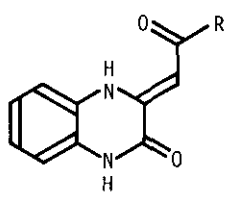
d. Spiroquinoxalines and Pyrido[1,2-a]quinoxalines

e. Quinoxalino[1',2':1,2]pyrido[4,3-b][1,5]benzodiazepine and Quinoxalinyl-1,2-diazepine

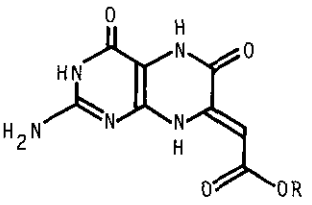
VI. Tautomeric Behaviors of 3-Heteroarylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxalines

I. INTRODUCTION

According to some reviews,[1,2,3] various quinoxaline derivatives have been prepared mainly by the following methods; (i) condensation of aromatic o-diamines and α-dicarbonyl compounds, (ii) intramolecular cyclization of N-substituted aromatic o-diamines, (iii) ring transformations of benzodiazepines, (iv) quinoxaline N-oxides from benzofurazan 1-oxides and o-quinone dioximes. By means of the above method (i), early in 1960s, the reaction of o-phenylenediamines with acetylenedicarboxylates was reported to give 3-alkoxycarbonylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxalines 1a,b by Iwanami.[4] Thereafter, tautomeric behaviors of 1a,b and related compounds 1c,d, and 2 have been studied by NMR and UV spectroscopies, that is, there are tautomeric equilibria in the enaminocarbonyl moiety of 1[5,6] and 2[7] (Scheme 1). The principle for the chemical modifications and transformations of 1a,b principally based on the above tautomeric nature. In 1972, Chapman[8] reported



1a R=OMe
1b R=OEt
1c R=Me
1d R=COOEt



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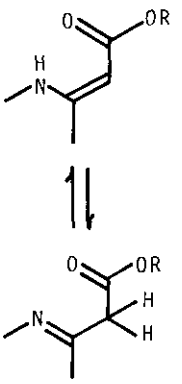
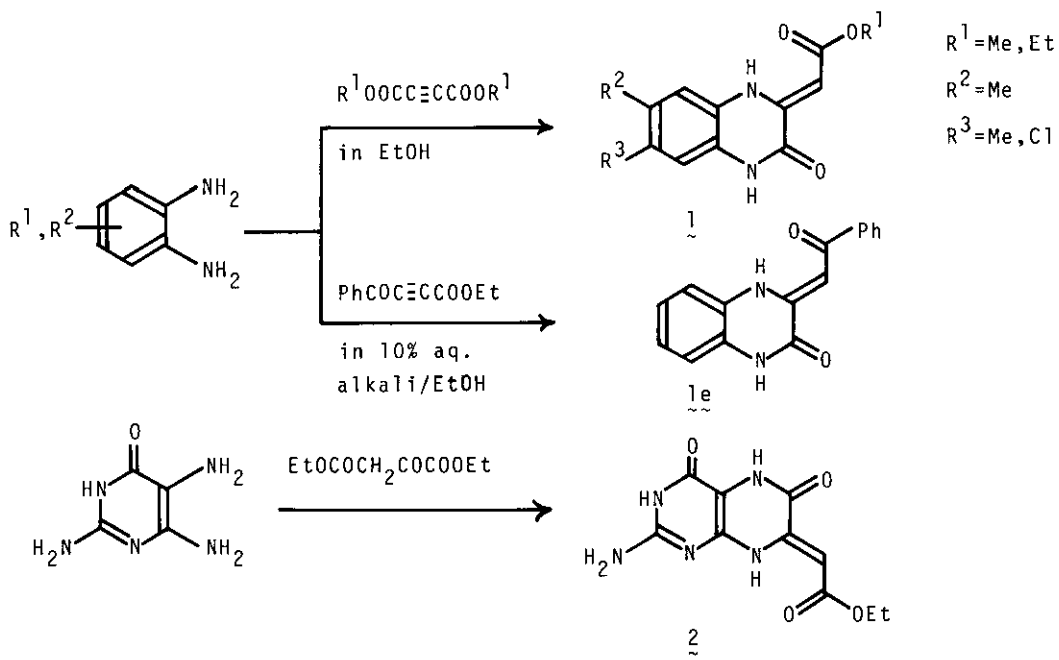


SCHEME 1

the chemical conversion of 1 into the condensed and noncondensed quinoxaline derivatives. Recently, Danswan et al.,[9] Kawahara et al.,[10] and the authors have presented some synthetic routes of 1 into a variety of quinoxalines. However, the quinoxaline synthesis utilizing 1 as the starting materials has not been reviewed so far, so that the results published by the above researchers are summarized as follows.

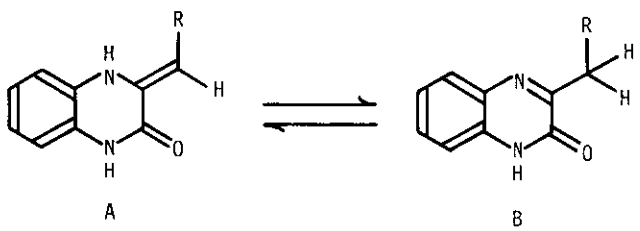
II. SYNTHESIS AND SPECTRAL PROPERTIES OF STARTING MATERIALS AND RELATED COMPOUNDS

3-Alkoxycarbonylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxalines (1a, R^1=Me R^2=R^3=H; 1b, R^1=Et R^2=R^3=H) are easily synthesized by the reaction of o-phenylenediamines with dimethyl and diethyl acetylenedicarboxylates in ethanol, in almost quantitative yields.[4] o-Phenylenediamine also reacts with β,γ-acetylenic-α-ketoacid ester in the presence of aqueous base to afford 2-phenacyl-3-quinoxalinone 1e in 83% yield.[11] The reaction of 2,5,6-triamino-4-oxo-3,4-dihydropyrimidine with diethyl oxaloacetate produced ethyl 2-(9-xanthopteryl)-acetate 2[7a] (Scheme 2).



SCHEME 2

Compounds 1a-d[5] and 1e[12,13] exhibited the tautomeric equilibria, which depend on kinds of solvents[5] and temperature of solutions[14] (Scheme 3). The NMR spectra in DMSO-d_6 manifested that two tautomers A and B (Scheme 3) coexisted in 1a,b, and the tautomer A was predominant in 1c,d, as shown in Table I. In addition, the NMR spectra in trifluoroacetic acid (TFA) clarified that 1a,b existed as the tautomer B, 1d,e as the tautomer A. Thus, the equilibria of 1a,b are proved to incline to the tautomer B in acidic media. This tendency is applied to the reaction of methylenic carbon of 1a,b with electrophilic reagents.



SCHEME 3 Equilibria of 1 in DMSO-d_6 or TFA

TABLE I. Tautomers of 1 assigned on the Basis of NMR Spectral Data

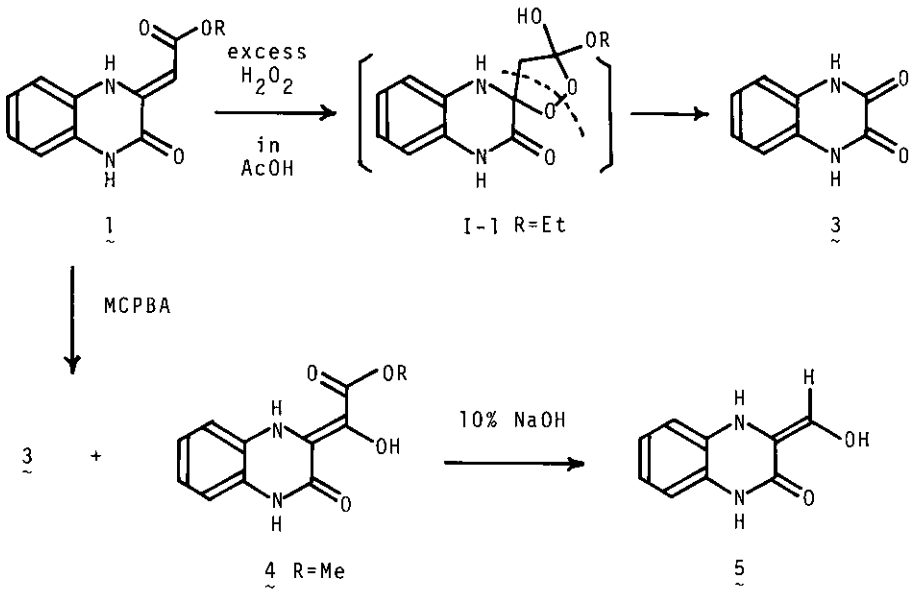
Compound			Tautomer	
No.	R	R'	in DMSO-d_6	in TFA
1a	COOMe	H	A B	B
1b	COOEt	H	A B	B
1c	COMe	H	A	A
1d	COCOOEt	Me	A	A

III. OXIDATION AND HALOGENATION OF STARTING MATERIALS

1. OXIDATION WITH m-CHLOROPERBENZOIC ACID AND HYDROGEN PEROXIDE/ACETIC ACID

Compound 1 is susceptible to oxidation with m-chloroperbenzoic acid (MCPBA) and H_2O_2. The reaction of 1b with an excess of H_2O_2 in AcOH provided 2,3-dioxo-1,2,3,4-

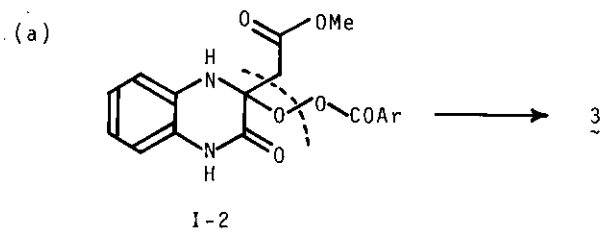
tetrahydroquinoxaline 3 (60%), presumably via an intermediate I-1,[15] while oxidation of 1a with MCPBA produced the methylenic C-hydroxylated compound 4 (40%) and 3 (9%)[16] (Scheme 4). Treatment of 4 with 10% NaOH furnished 3-hydroxymethylene-2-oxo-1,2,3,4-tetrahydroquinoxaline 5 (70%). The reaction mechanism of 1a to 3 and 4 is shown in Scheme 5, including intermediates I-2, I-3, and I-4.



1 I-1 R=Et 3

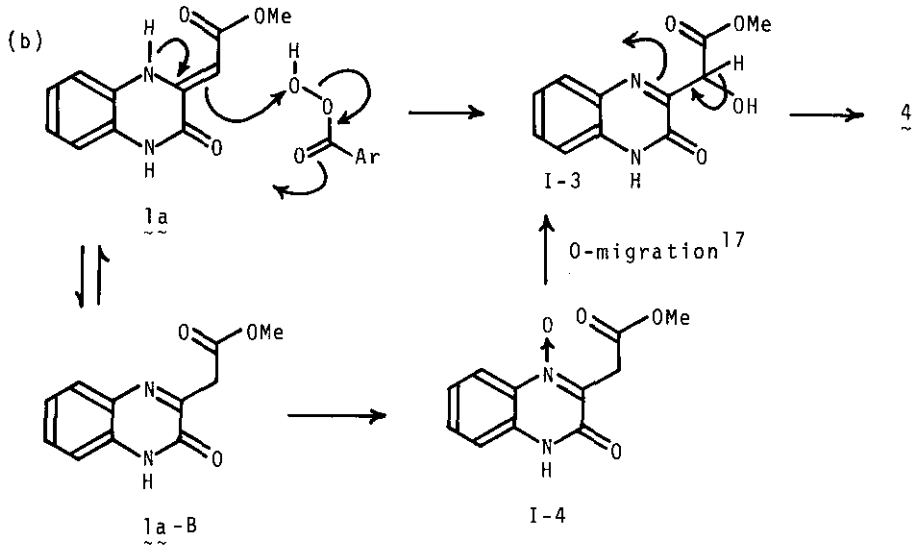
3 + 4 R=Me 5

SCHEME 4



I-2 3

SCHEME 5

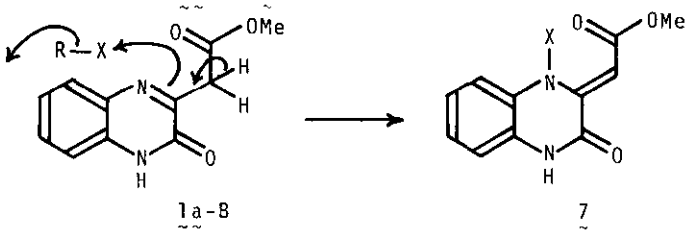


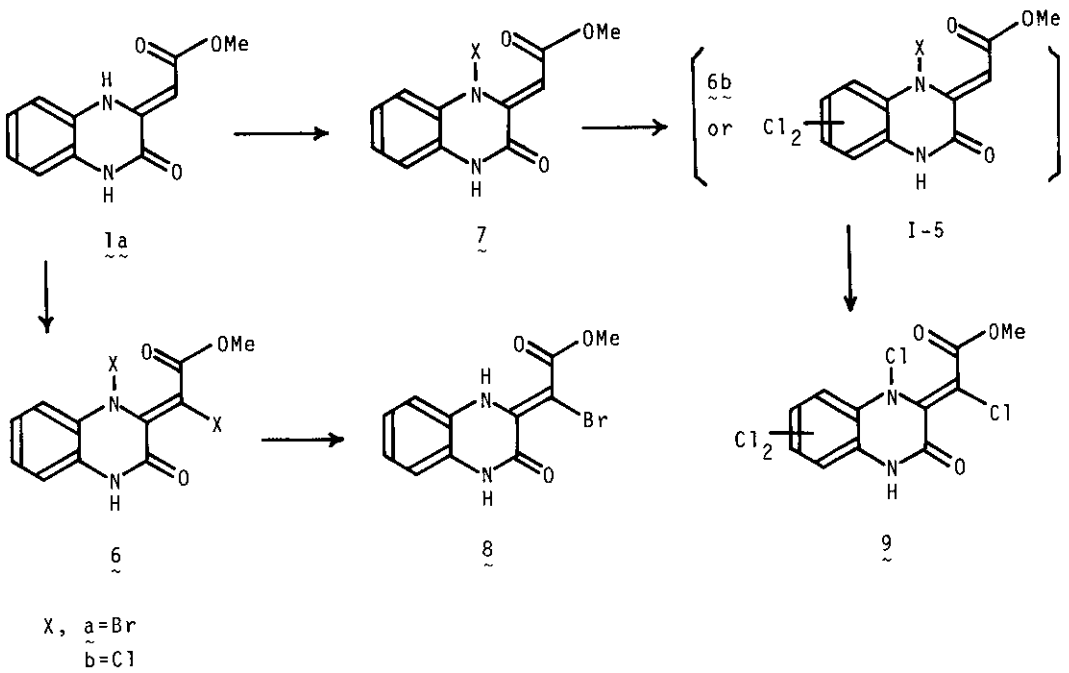
SCHEME 5

2. HALOGENATION

Although MCPBA and H_2O_2/AcOH acted as the oxidizing agent for 1a,b, the reactions of 1a with H_2O_2/HBr and H_2O_2/HCl resulted in the formations of N^4- and methylenic C-dihalogenated compounds 6a (87%) and 6b (70%)[18] (Scheme 6). On the other hand, the reactions of 1a with Br_2/H_2O, Cl_2/H_2O, and N-halogenosuccinimide (NBS, NCS) resulted in N^4-halogenations to give compounds 7a,b (95-99%). Compound 6b was also obtained by the reaction of 4 with H_2O_2/HCl in 63% yield. N^4-Debromination of 6a was successful by treatment with ZnI_2 in AcOH/TFA, affording the monobromo compound 8 (41%). Further chlorination of 7b with H_2O_2/HCl provided the tetrachlorinated compound 9 (27%), presumably via 6b or trichlorinated intermediate I-5. These reaction mechanisms were also proposed as follows.

(a) mechanism from 1a to 7

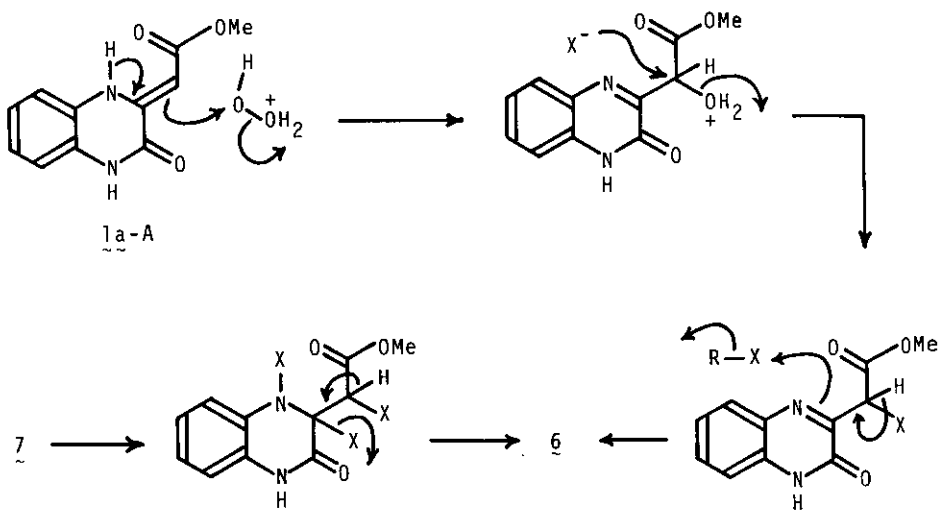




X, a=Br
b=Cl

SCHEME 6

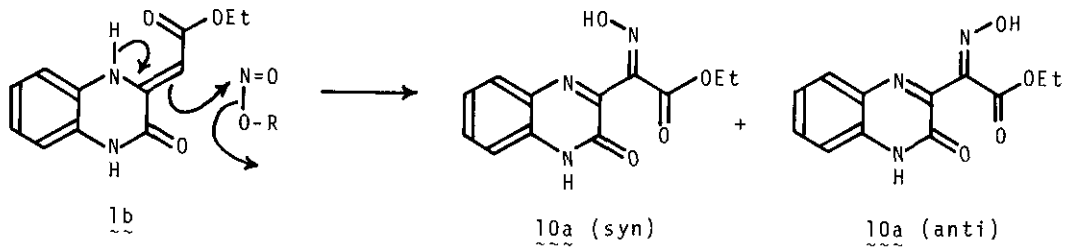
(b) mechanism from 1a to 6



VI. SYNTHESIS OF KEY INTERMEDIATES

1. ETHYL 2-(3,4-DIHYDRO-3-OXO-2-QUINOXALINYL)-2-HYDROXYIMINOACETATE

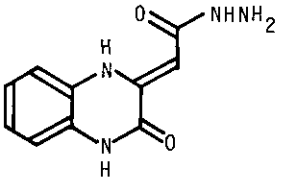
The reaction of 1b (23.2 g) with isopentyl nitrite (15 g) in trichloroacetic acid (3 g)/AcOH (500 ml) at room temperature resulted in methylenic C-hydroxyimination[19] to produce ethyl 2-(3,4-dihydro-3-oxo-2-quinoxalinyl)-2-hydroxyiminoacetate (10a) [10a (syn) (9.5 g), 10a (anti) (14 g)][8] (Scheme 7).



SCHEME 7

2. 3-HYDRAZINOCARBONYLMETHYLENE-2-OXO-1,2,3,4-TETRAHYDROQUINOXALINE

The reaction of 1a (10 g) with 10-fold molar excess of hydrazine hydrate (22.95 g) in EtOH (200 ml) under reflux easily provided 3-hydrazinocarbonylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxaline 11 (9.80 g, 98%).[20]



11

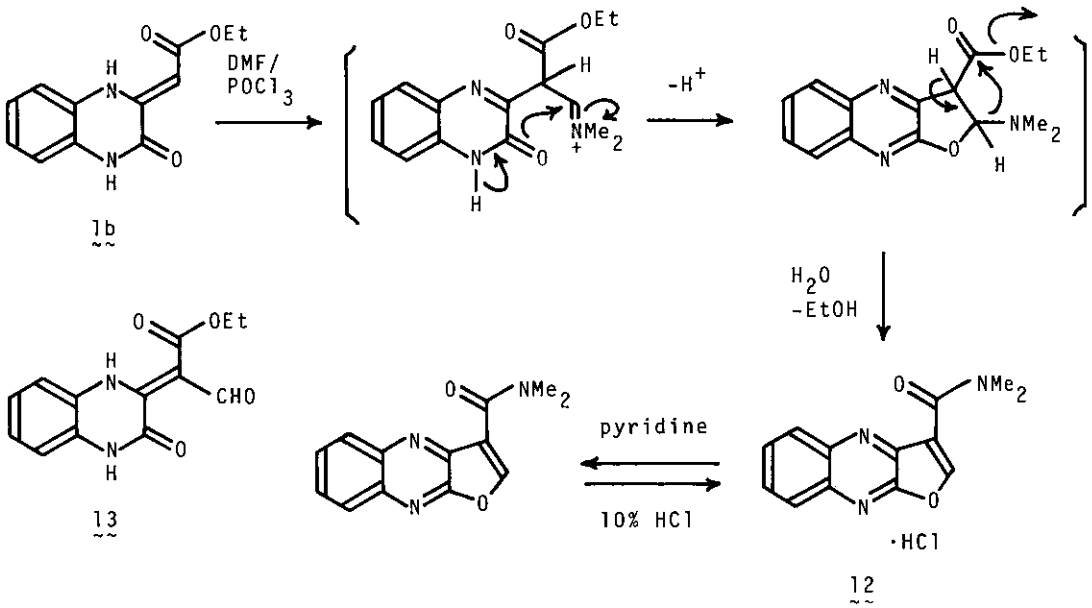
3. 3-(N,N-DIMETHYLCARBAMOYL)FURO[2,3-b]QUINOXALINE HYDROCHLORIDE

The reaction of 1b (10 g) with $POCl_3$ (100 ml)/DMF (100 ml) under heating on a boil-

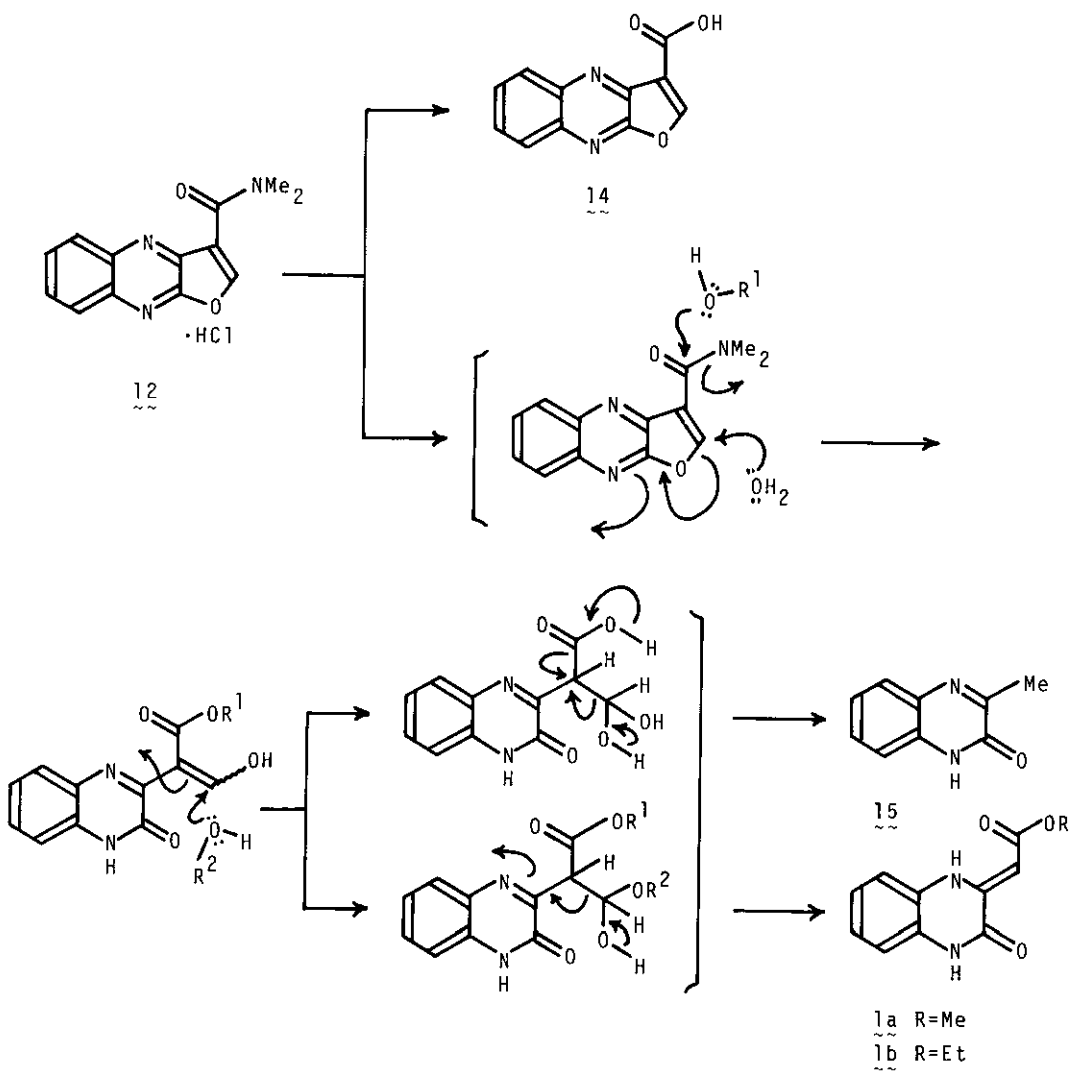
ing water bath furnished 3-(N,N-dimethylcarbamoyl)furo[2,3-b]quinoxaline hydrochloride 12 (9.93 g, 83%), whereas the methylenic C-formylated compound 13 was not obtained[21] (Scheme 8).

Compound 12 is susceptible to attack with nucleophiles. For example, its heating in aqueous alcohol, aqueous AcOH, 10% NaOH, 10% HCl provided furo[2,3-b]quinoxaline-3-carboxylic acid 14, 3-methyl-2-oxo-1,2-dihydroquinoxaline 15,[22] and 1. These results are represented in Scheme 9 and Table II.[21b] Predominant hydrolysis of 12 into 14 in AcONa/AcOH and pyridine/AcOH may be due to a moisture in the reaction media.

The above three key intermediates 10, 11, and 12 have been the source materials leading to a plenty of novel quinoxaline derivatives, and the conversions of 10, 11, and 12 are described below.



SCHEME 8



SCHEME 9

TABLE II. Conversion of 12 into Quinoxaline Derivatives

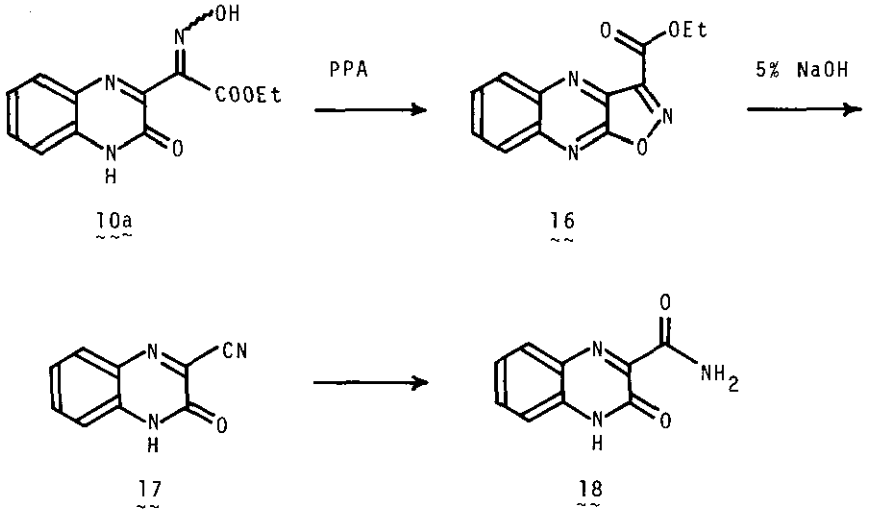
Reaction Medium	Product (Yield %)	Reaction Medium	Product (Yield %)	
AcONa/AcOH	14 (86)	80% aq. AcOH	15 (17)	14 (39)
Pyridine/AcOH	14 (78)	EtONa/EtOH	1b (95)	
10% NaOH	15 (95)	80% aq. EtOH	1b (80)	14 (19)
10% HCl	15 (60)	80% aq. MeOH	1a (40)	14 (57)

V. SYNTHESIS OF QUINOXALINES FROM KEY INTERMEDIATES

1. PREPARATION OF ISOXAZOLE, TRIAZOLE, AND IMIDAZOLE RING-CONDENSED QUINOXALINES

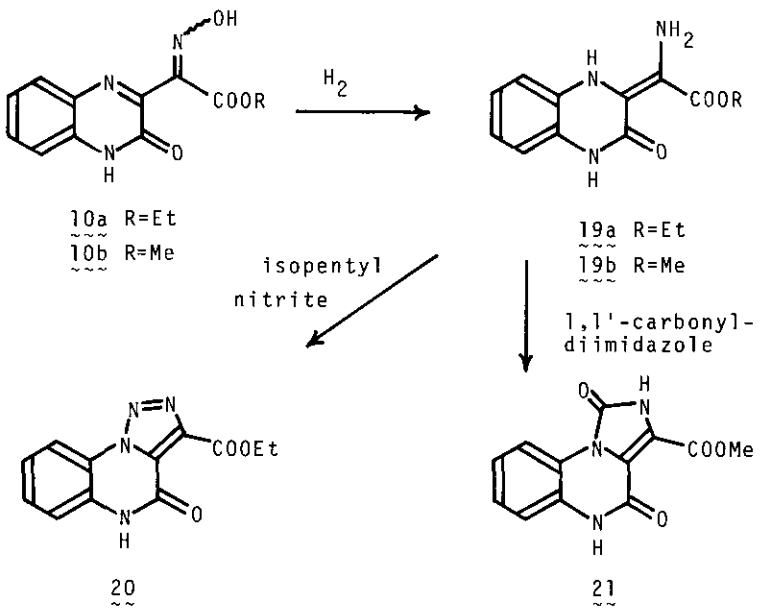
Ring closure of 10a to isoxazole ring could be accomplished for the syn and anti isomers by heating in polyphosphoric acid (PPA), giving the isoxazolo[4,5-b]quinoxaline 16 in good yields[8] (Scheme 10). Treatment of 16 with 5% NaOH formed the nitrile 17 (99%), while prolonged base treatment of 16 afforded the amide 18.

The hydroxyimino compounds 10a,b were also applicable for the preparation of the 1,2-fused quinoxalines such as v-triazolo[1,5-a]quinoxalines and imidazo[1,5-a]-quinoxalines. Namely, catalytic reductions of 10a,b provided the amino compounds 19a and 19b, which were cyclized with isopentyl nitrite and 1,1'-carbonyldiimidazole to produce the v-triazolo[1,5-a]quinoxaline-3-carboxylate 20[8] and 1,4-dioxo-imidazo[1,5-a]quinoxaline-3-carboxylate 21,[9] respectively (Scheme 11).



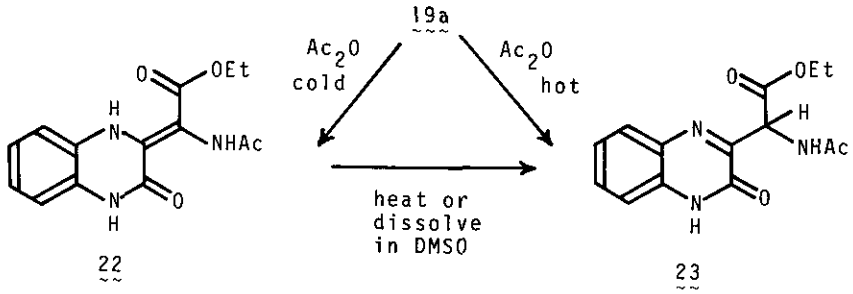
10a 16 17 18

SCHEME 10



SCHEME 11

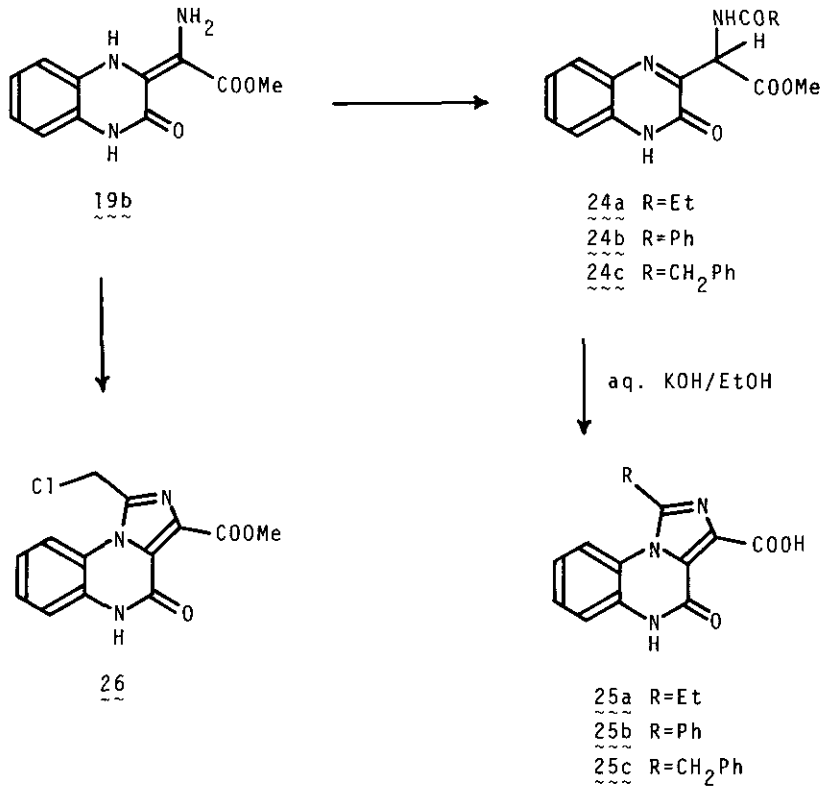
Although 19a could not be purified by recrystallization owing to decomposition, its structure was established by the spectral properties and an examination of its acetylation products (Scheme 12). The acetate 22 was obtained under cold condition, while its isomeric acetate 23 under hot condition.[8] Moreover, heating of 22 isomerized to the stable 23, and this isomerization was also confirmed when the NMR spec-



SCHEME 12

trum was measured in DMSO.

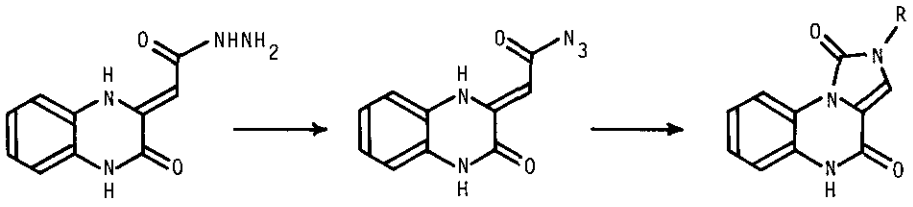
Compound 19b was also converted into the C^1-substituted imidazo[1,5-a]quinoxalines (Scheme 13).[9] Acylation of 19b furnished the N-acyl derivatives 24a (81%), 24b (66%), and 24c (66%), which cyclized into the corresponding C^1-substituted imidazo-[1,5-a]quinoxaline-3-carboxylic acids 25a (60%), 25b (52%), and 25c (47%) by heating in KOH solution. 1-Chloromethyl derivative 26 was obtained by the reaction of 19b with triethyl orthochloroacetate in 72% yield.



SCHEME 13

2,4-Dioxoimidazo[1,5-a]quinoxalines (type 21 in Scheme 11) were also obtained from the key intermediate 11 (Scheme 14).[23] The reaction of 11 with an equimolar amount of HNO_2 gave the azide 27 (98%), whose refluxing in xylene and in Ac_2O afforded the 1,4-dioxoimidazo[1,5-a]quinoxaline 28a (98%) and the N^2-acetyl derivative 28b (88%),

respectively. Acetylation of 28a with Ac_2O provided 28b in 88% yield.



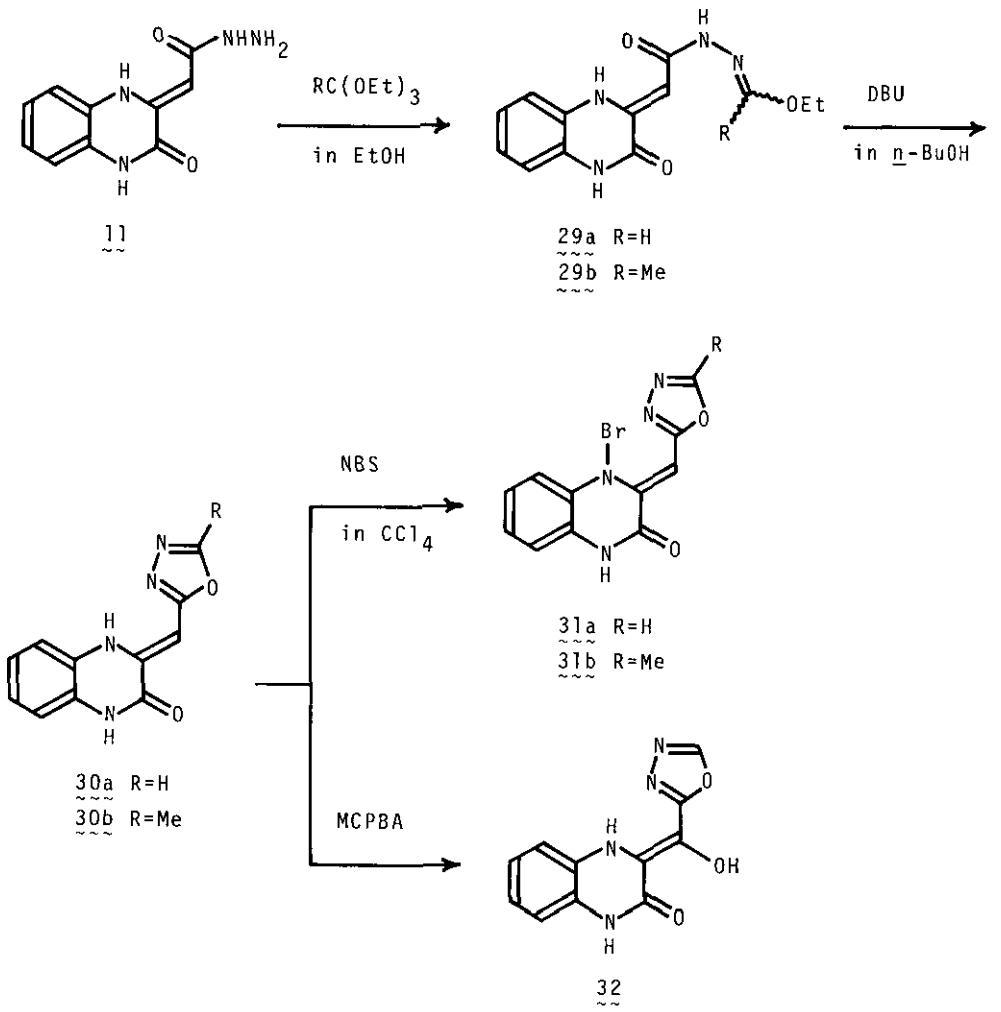
SCHEME 14

2. PREPARATION OF HETEROCYCLEMETHYLENE- AND HETEROCYCLE-CONJUGATED QUINOXALINES

Hereupon, the syntheses of the azolylmethylene- and azole-conjugated quinoxalines are described, wherein the azoles are 1,3,4- and 1,2,4-oxadiazoles, 1,2,4-triazoles, and pyrazolones, which have been known to possess biological activities.[20b,24] The reactions of 11 with orthoesters in EtOH produced the hydrazones 29a,b (98%), whose refluxing in 1,8-diazabicyclo[5,4,0]-7-undecene (DBU)/n-BuOH resulted in the formations of the 1,3,4-oxadiazolylmethylenequinoxalines 30a,b (91%)[20] (Scheme 15). The structures of 30a,b were established by the spectral data and ascertained by the following reactions. That is, the reactions of 30a,b with NBS gave the N^4-brominated derivatives 31a (74%) and 31b (86%), and the reaction of 30a with MCPBA formed the methylenic C-hydroxylated compound 32 (22%) (cf. section III).

When 29a,b were refluxed in DMF, interesting results were obtained (Scheme 16). Compound 29a (R=H) cyclized to the pyrazolylquinoxaline 33a (86%), which would be promoted by the tautomerization from 1A to 1B type with DMF (cf. Scheme 3). On the contrary, 29b (R=Me) was transformed into 30b (60%), wherein the steric hindrance by methyl group would block the cyclization into the pyrazolone ring.

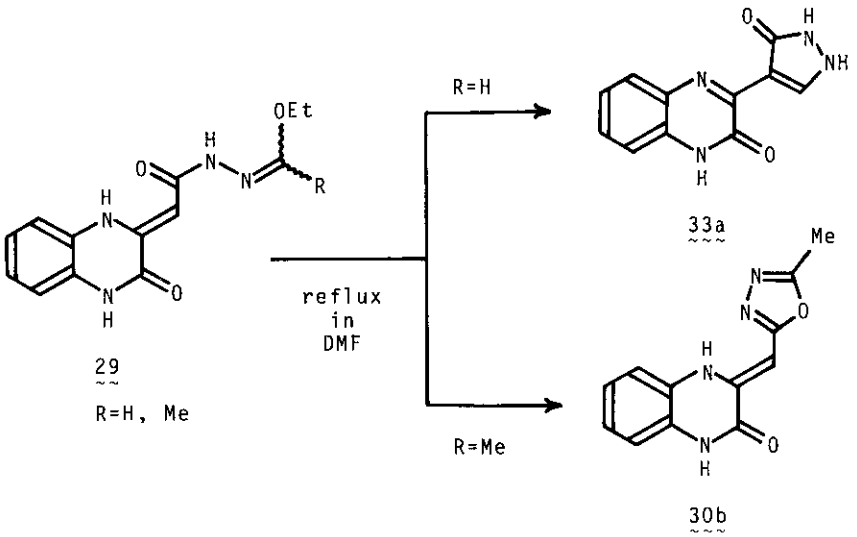
As described above, the selective cyclizations are found to depend on the kinds of solvents. In relation to the above results, CS_2 was employed as a one-carbon reagent in order to prepare the 30 and 33 types of compounds having the S-functional



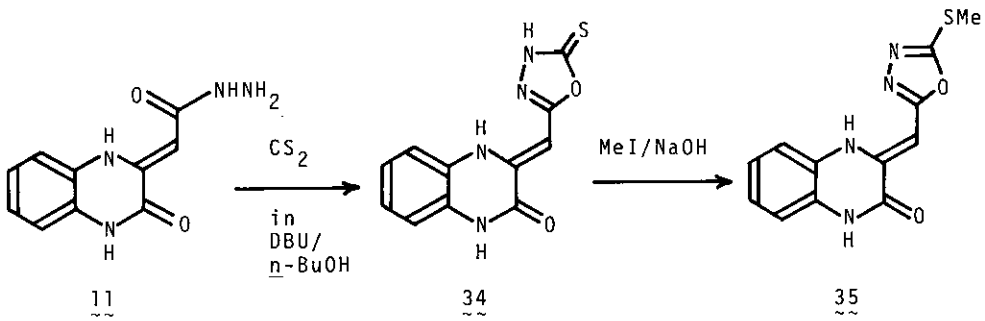
SCHEME 15

groups. The reaction of 11 with CS_2 in DBU/n-BuOH afforded the 2-thioxo-1,3,4-oxadiazolylmethylenequinoxaline 34 (83%), whose methylation with MeI/NaOH provided the thiomethyl derivative 35 (80%)[25] (Scheme 17).

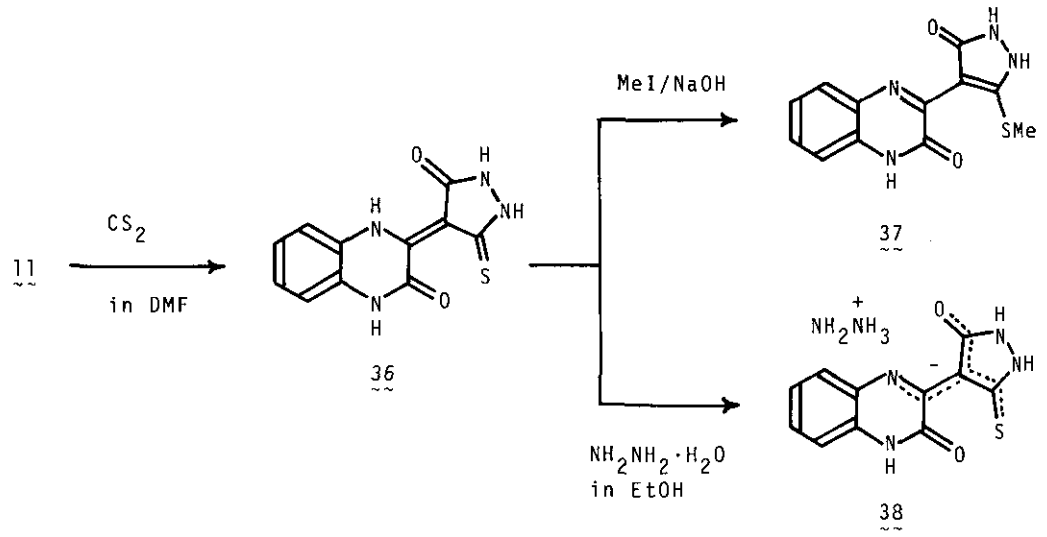
On the other hand, the reaction of 11 with CS_2 in DMF provided the 3-oxo-5-thioxopyrazolylidenequinoxaline 36 (72%), whose methylation furnished the S-methylated compound 37 (91%). Refluxing of 36 and hydrazine hydrate in EtOH formed the hydrazinium salt 38 (92%)[25] (Scheme 18).



SCHEME 16



SCHEME 17

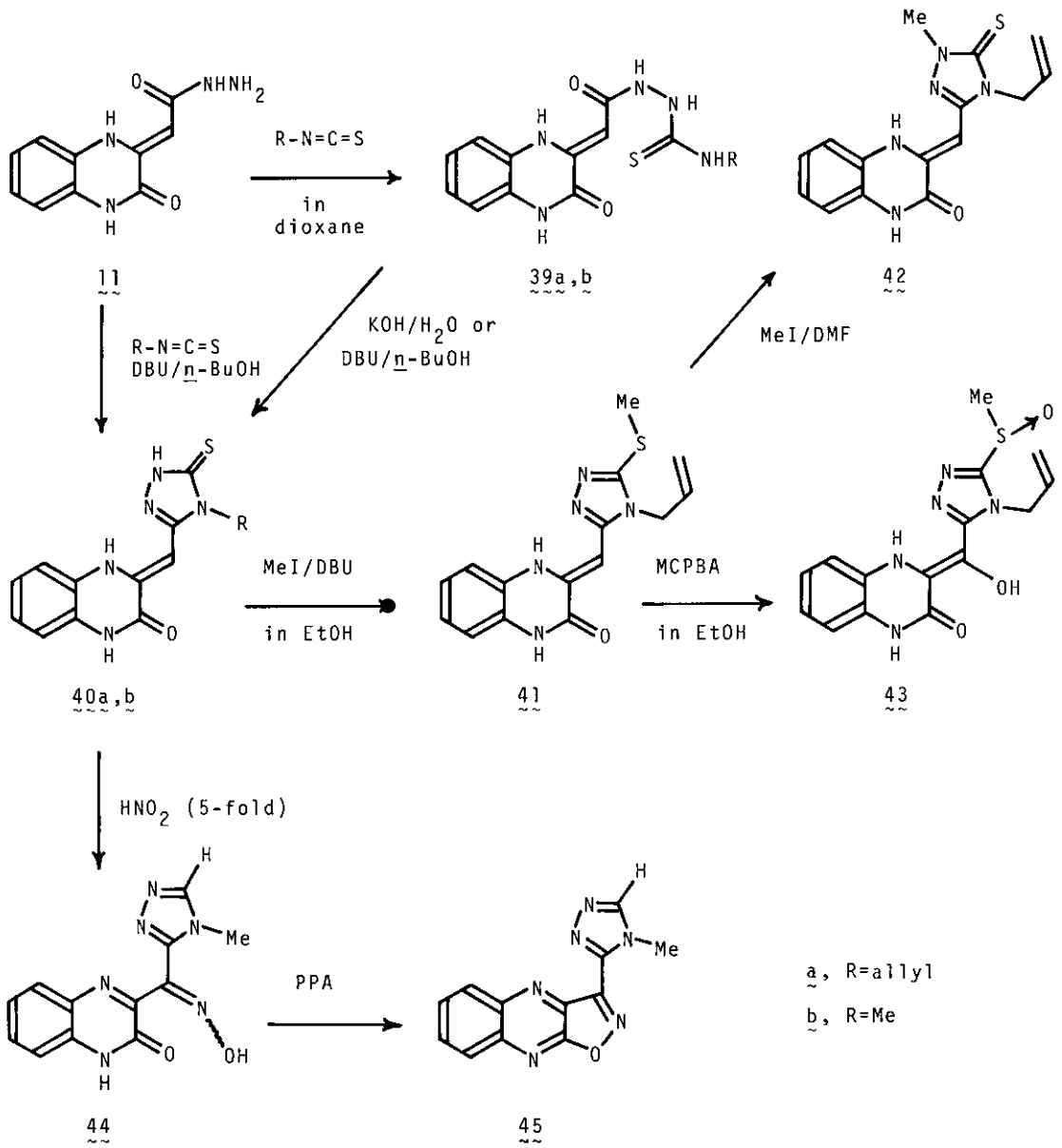


SCHEME 18

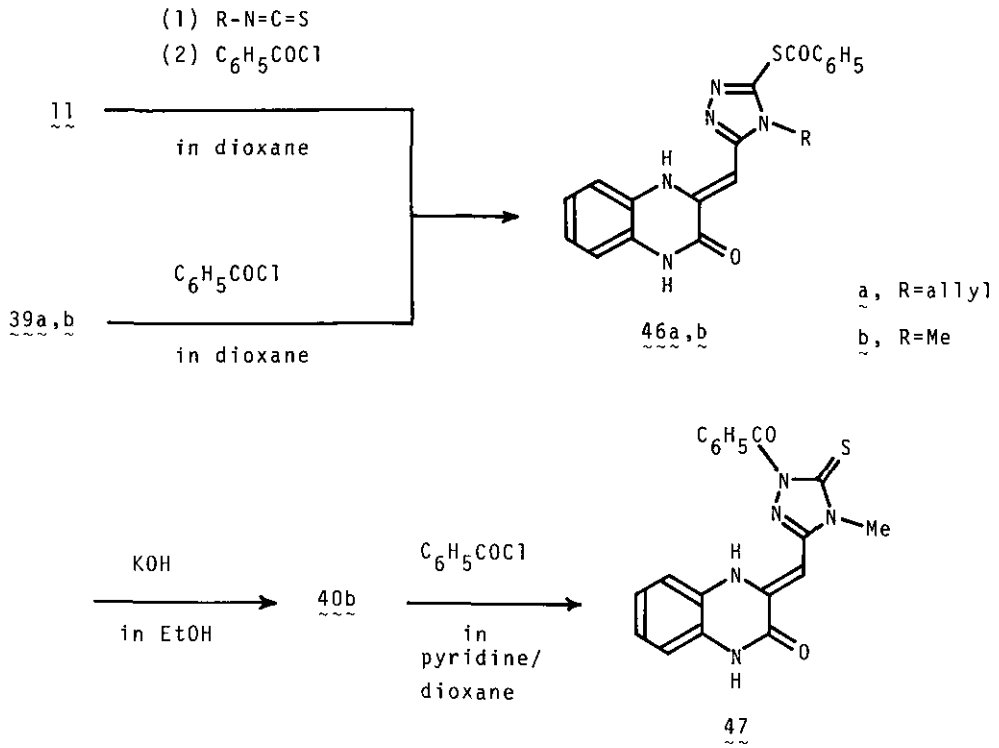
Moreover, when isothiocyanates were incorporated into 11, 1,2,4-triazolylmethylenequinoxalines were obtained[24] (Scheme 19). The reactions of 11 with isothiocyanates (a, R=allyl; b, R=Me) in dioxane gave the thiosemicarbazides 39a (94%) and 39b (97%), respectively, whose treatments with bases such as DBU and aq. NaOH afforded the 3-thioxo-1,2,4-triazolylmethylenequinoxalines 40a (86%) and 40b (93%), respectively. Compounds 40a,b were also obtained directly by the reactions of 11 with isothiocyanates in DBU/n-BuOH in 69% and 82% yields, respectively. Methylation of 40a with MeI/DBU provided the thiomethyl derivative 41 (76%), whose further refluxing in MeI/DMF furnished the N-methyl derivative 42 (46%). On the other hand, oxidation of 41 with MCPBA (2 eq.) formed the methylenic C-hydroxylated methylsulfinyl derivative 43 (18%).[24b]

The reaction of 40 with HNO_2 gave the hydroxyimino compound 44 (66%), whose heating in PPA afforded the 3-(1,2,4-triazolyl)isoxazolo[4,5-b]quinoxaline 45 (40%).

The thiosemicarbazides 39 also cyclized to the 1,2,4-triazole ring with benzoyl chloride.[26] Refluxing of 39a,b in benzoyl chloride/dioxane provided the S-benzoylated 1,2,4-triazoles 46a (32%) and 46b (32%), respectively (Scheme 20). When they


R-N=C=S
in dioxane
KOH/H2O or DBU/n-BuOH
R-N=C=S DBU/n-BuOH
MeI/DMF
MeI/DBU
in EtOH
MCPBA
in EtOH
HNO2 (5-fold)
PPA
11
39a,b
42
40a,b
41
43
44
45
a, R=allyl
b, R=Me

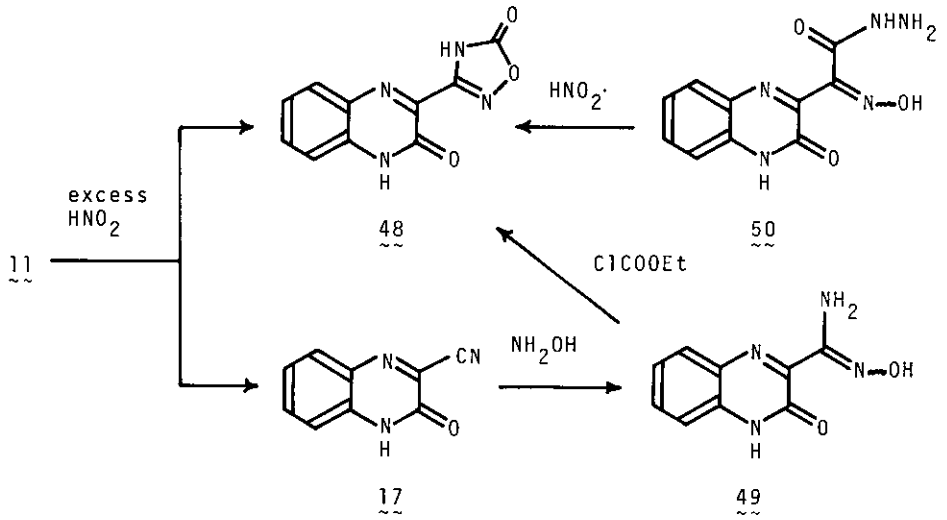
SCHEME 19



SCHEME 20

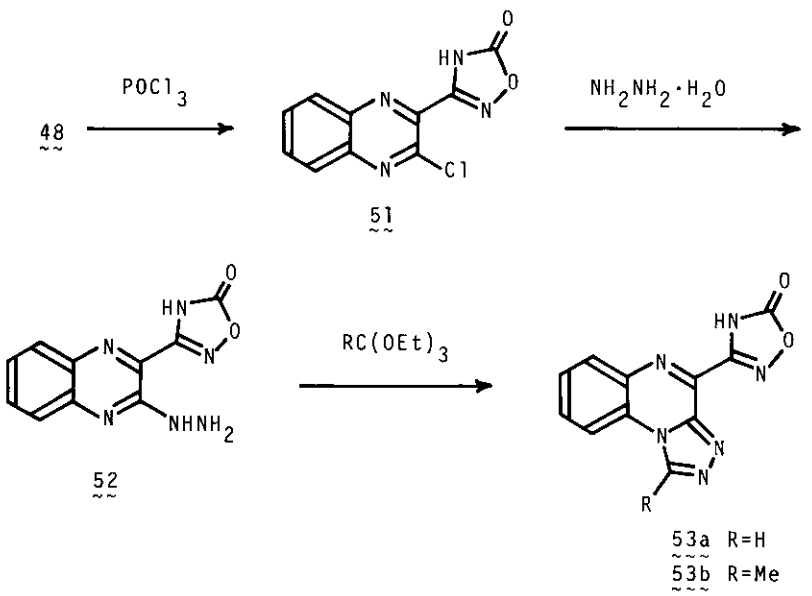
were prepared from 11 by one-pot reaction, the yields of 46a and 46b were 31% and 40%, respectively. Treatment of 46b with KOH furnished 40b, whose benzoylation with benzoyl chloride in pyridine/dioxane formed the N-benzoylated derivative 47 (44%).

As depicted in Scheme 14, the reaction of 11 with an equimolar amount of HNO_2 led to the production of the imidazo[1,5-a]quinoxalines 28a,b. However, a 5-fold molar excess of HNO_2 converted 11 into 1,2,4-oxadiazolylquinoxaline 48 (60%) and the nitrile 17 (27%)[28] (Scheme 21). A 2-fold molar amount of HNO_2 predominantly gave 48 (90%). Compound 48 was unambiguously synthesized from 17. Namely, addition of NH_2OH to 17 afforded the carboxamide oxime 49 (96%), whose reaction with ethyl chlorocarbonate provided 48 (79%). Furthermore, the reaction of the key intermediate 10 with hydrazine hydrate formed the hydrazide 50 (93%), whose reaction with



SCHEME 21

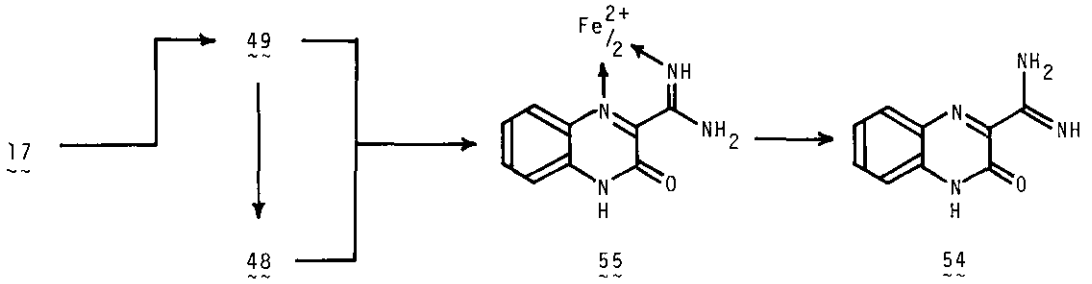
HNO_2 provided 48 (69%). Compound 48 was further derivatized, as shown in Scheme 22. Chlorination of 48 with $POCl_3$/DMF formed the monochloride 51 (92%), whose re-



SCHEME 22

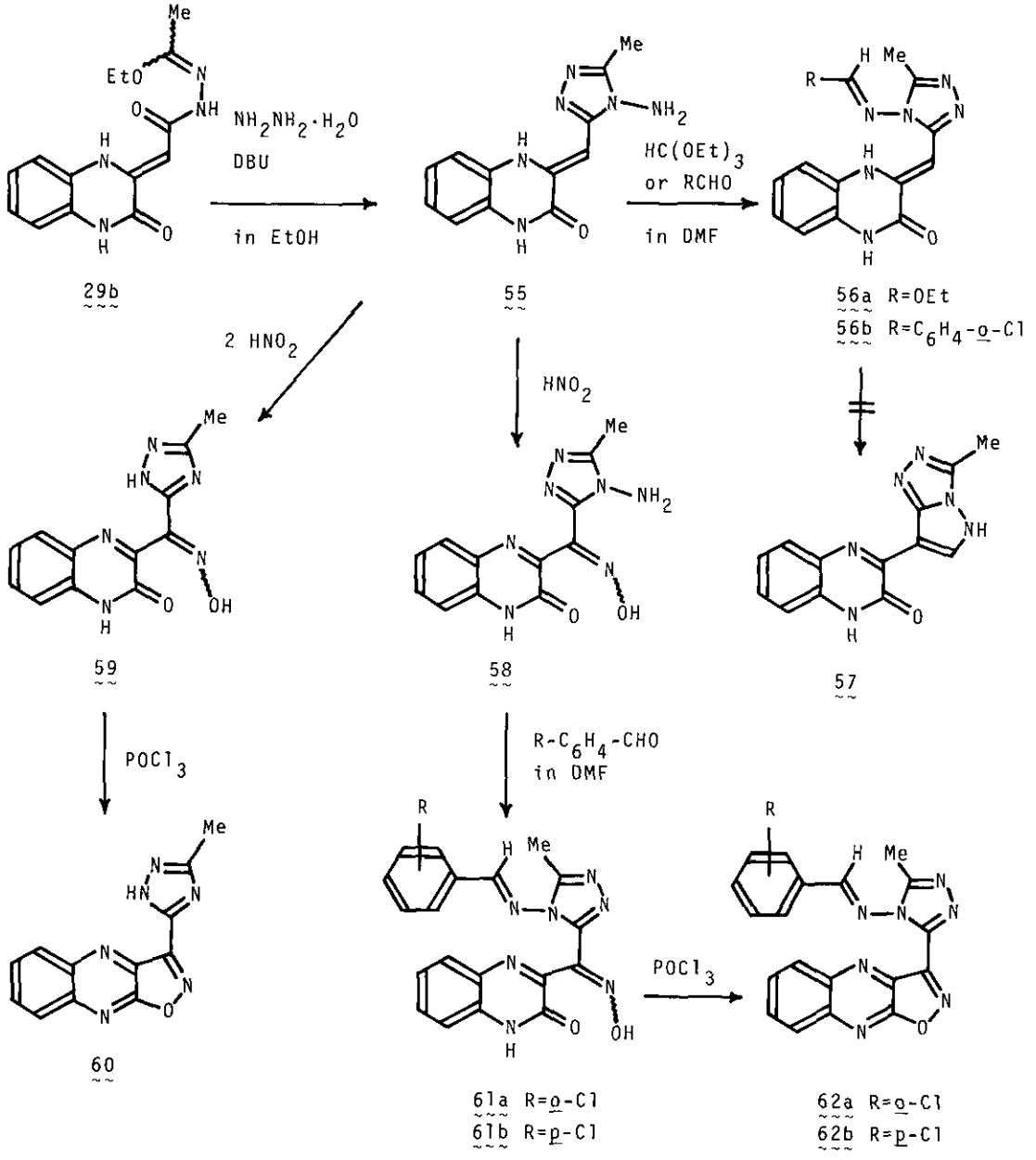
action with an excess of hydrazine hydrate gave the hydrazide 52 (99%). Refluxing of 52 in orthoesters/n-BuOH afforded the s-triazolo[4,3-a]quinoxalines 53a (98%) and 53b (83%).

Moreover, the route of the nitrile 17 to the 2-amidinoquinoxaline 54 could be developed[29] (Scheme 23). As displayed in Scheme 21, the nitrile 17 was converted into 48 via 49, and reductions of 48 and 49 with Fe/HCl/AcOH and $FeSO_4$/HCl/AcOH produced the Fe-complexes 55 (55-88%). Treatment of 55 with 10% NaOH furnished 54 (69-83%).



SCHEME 23

While the hydrazone 29b was converted into 1,3,4-oxadiazolylmethylenequinoxaline 30b (Scheme 15), 29b could also be the starting material to the 4-amino-4H-1,2,4-triazolylmethylenequinoxaline 55 (Scheme 24).[30] The reaction of 29b with hydrazine hydrate/DBU in ethanol formed the requisite compound 55 (80%). The reactions of 55 with triethyl orthoformate and o-chlorobenzaldehyde in DMF gave the substituted 4-amino-4H-1,2,4-triazoles 56a (84%) and 56b (45%), respectively. However, 56a did not cyclize into the pyrazolotriazole 57 (cf. Scheme 16). The reactions of 55 with an equimolar and 2-fold molar amount of HNO_2 afforded the hydroxyimino derivative 58 (79%) and the deaminated hydroxyimino compound 59 (97%). The structure of 59 was assumed to be the 1H-1,2,4-triazole form.[31] Refluxing of 59 in $POCl_3$ formed the 3-(5-triazolyl)isoxazolo[4,5-b]quinoxaline 60 (88%). Moreover, the reactions of 58 with o- and p-chlorobenzaldehydes provided the 4-benzylideneamino-4H-1,2,4-triazoles 61a (76%) and 61b (41%), respectively, whose refluxing in $POCl_3$ resulted in dehydrative cyclization to produce the isoxazolo[4,5-b]quinoxaline derivatives



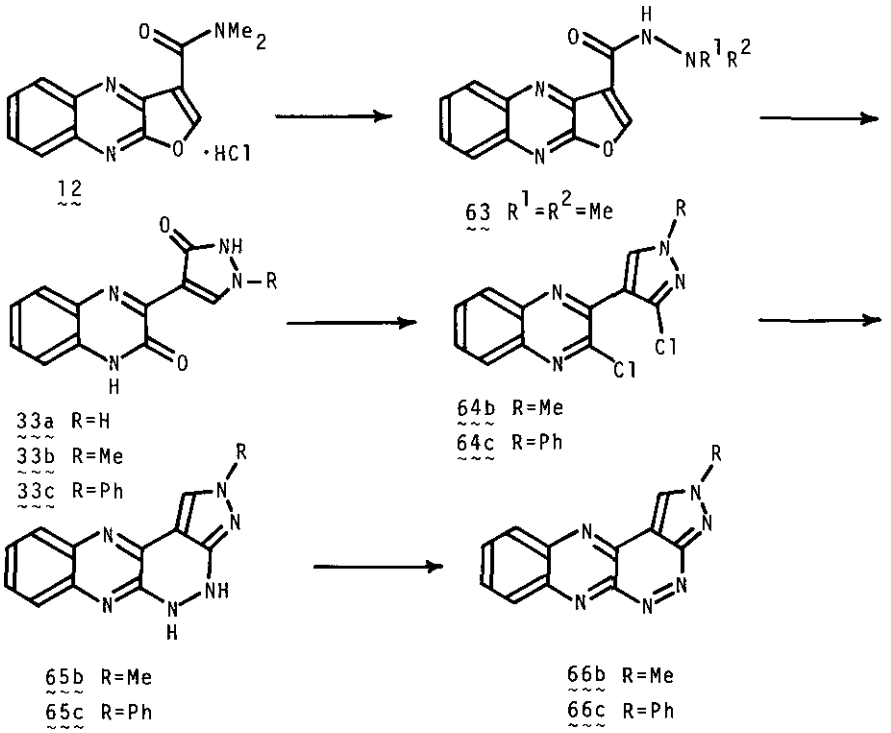
SCHEME 24

62a (76%) and 62b (91%), respectively.

3. PREPARATION OF VARIOUS QUINOXALINES BY RING TRANSFORMATIONS

a. PYRAZOLYLQUINOXALINES AND PYRAZOLO[3',4':3,4]PYRIDAZINO[5,6-b]QUINOXALINES

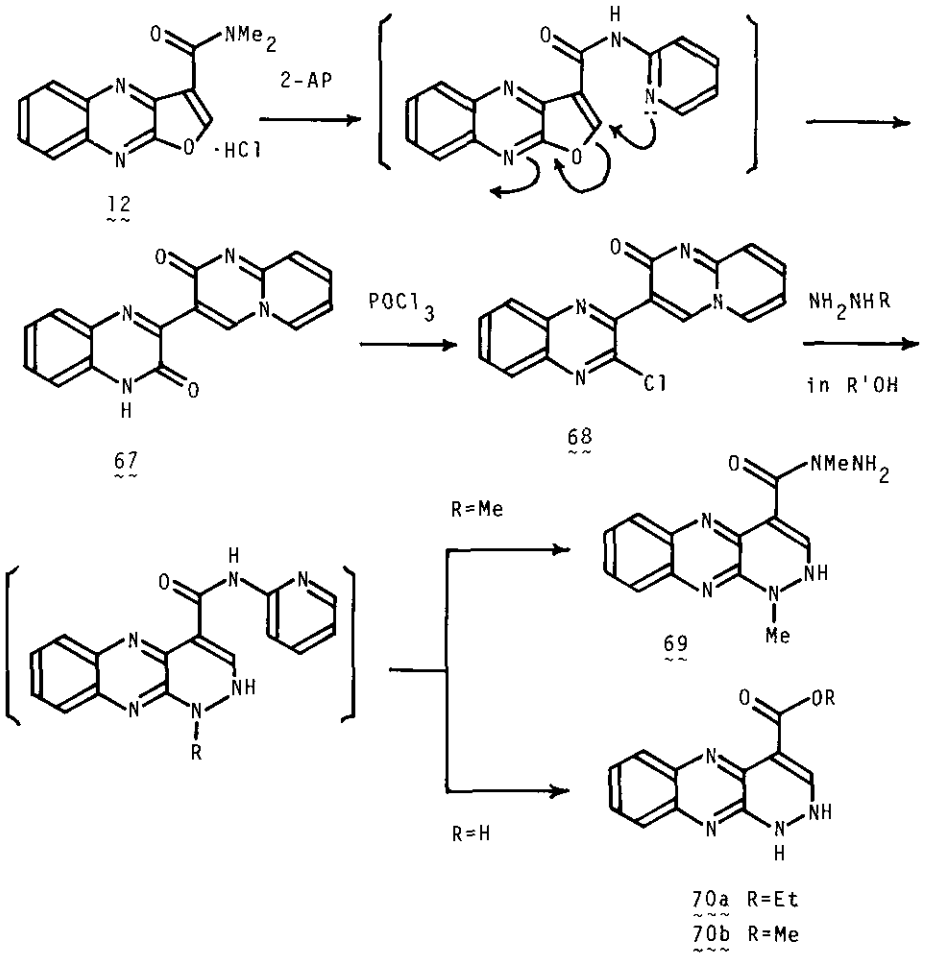
The reaction of 12 with 1,1-dimethylhydrazine afforded the hydrazide 63 (92%), while its reaction with hydrazine hydrate, methylhydrazine, and phenylhydrazine resulted in ring transformation to provide the pyrazolylquinoxalines 33a-c (85-96%)[21] (Scheme 25). Chlorinations of 33b (R=Me) and 33c (R=Ph) with $POCl_3$/DMF formed the dichlorides 64b (90%) and 64c (50%), respectively. Refluxing of 64b and 64c in hydrazine hydrate produced the dihydropyrazolo[3',4':3,4]pyridazino[5,6-b]quinoxalines 65b (80%) and 65c (87%), respectively, which were easily oxidized with dibenzyl azodicarboxylate to furnish 2-methylpyrazolo[3',4':3,4]pyridazino[5,6-b]quinoxaline 66b (86%) and 2-phenylpyrazolo[3',4':3,4]pyridazino[5,6-b]quinoxaline 66c (80%), respectively.



SCHEME 25

b. PYRIDO[1,2-a]PYRIMIDYLQUINOXALINE AND PYRIDAZINO[3,4-b]QUINOXALINES

The reaction of 12 with 2-aminopyridine (2-AP) effected ring transformation to form the pyrido[1,2-a]pyrimidylquinoxaline 67 (60%), whose reaction with $POCl_3$/DMF gave the chlorinated compound 68 (87%)[32] (Scheme 26). The reaction of 68 with methylhydrazine in EtOH further resulted in ring transformation to afford 1-methyl-4-(1-methylhydrazinocarbonyl)-1,2-dihydropyridazino[3,4-b]quinoxaline 69 (78%), while the reactions of 68 with hydrazine hydrate in EtOH and in MeOH provided the 4-alkoxycarbonyl-1,2-dihydropyridazino[3,4-b]quinoxalines 70a (92%) and 70b (82%), respectively.



SCHEME 26

c. *QUINOXALINYL-1,5-BENZODIAZEPINES AND BENZIMIDAZOLYLMETHYLENEQUINOXALINE*

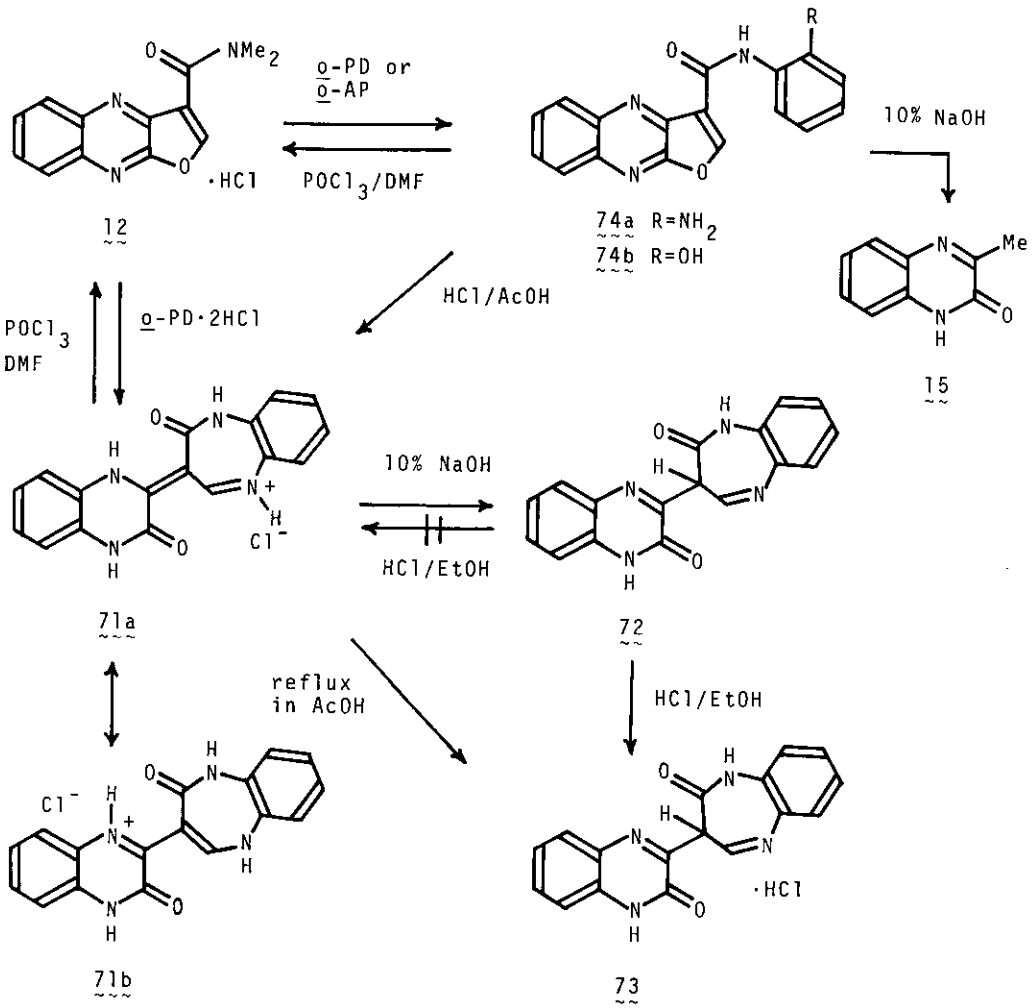
The reaction of 12 with o-phenylenediamine (o-PD) dihydrochloride effected ring transformation to produce the quinoxalinyl-1,5-benzodiazepine hydrochloride 71a or 71b (72%) (NH form), whose treatment with 10% NaOH produced the C^3-H isomer 72 (91%)[33] (Scheme 29). Further treatment of 72 with HCl/EtOH formed the hydrochloride of C^3-H isomer 73 (98%). Refluxing of 71 in AcOH also induced the isomerization to give 73 (73%). On the other hand, the reactions of 12 with o-phenylenediamine and o-aminophenol resulted in only substitution to afford the 3-(N-arylcarbamoyl)furo[2,3-b]quinoxalines 74a (81%) and 74b (98%), respectively. However, refluxing of 74a in HCl/AcOH effected ring transformation to provide 71 (39%), and a prolonged refluxing produced 73 (65%). Treatments of 74a and 74b with 10% NaOH formed 15 (46% from 74a; 46% from 74b). In the reaction with the Vilsmeier reagent, 71 was converted into 12, while 72 and 73 into the N^1-formyl-$C^{3'}$-chlorinated compound 75 (26% from 72; 68% from 73). In addition, 74a and 74b were also transformed into 12 (22% from 74a; 72% from 74b). Acetylation of 72 in Ac_2O gave the N^1-acetylated compound 76 (50%) (Scheme 30).[33]

Compound 71 was further transformed by refluxing in H_2O/AcOH, giving the benzimidazolylmethylenequinoxaline 77 hydrochloride (87%), whose treatment with 10% NaOH afforded the free base 77 (93%)[34] (Scheme 31). The reaction of 77 with HNO_2 provided the hydroxyimino compound 78 (91%), whose cyclization with $POCl_3$ produced the isoxazolo[4,5-b]quinoxaline 79 (96%). In addition, the reaction of 77 with MCPBA (2 eq.) furnished the ketone 80 (49%), whose reaction with o-phenylenediamine dihydrochloride followed by treatment with 10% NaOH gave the quinoxalino[2,3-b][1,5]-benzodiazepine 81 (27%).

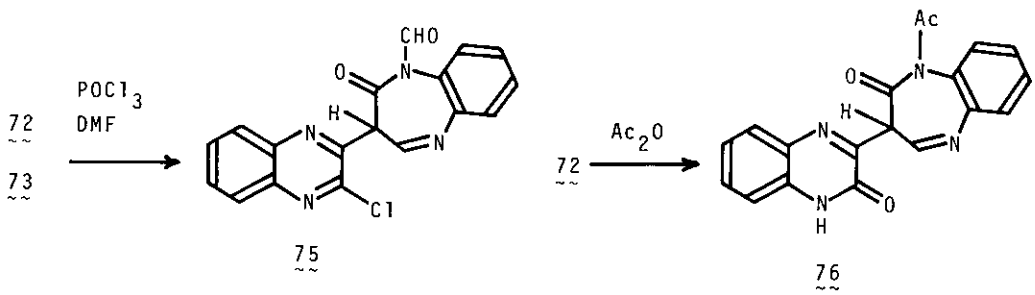
d. *SPIROQUINOXALINES AND PYRIDO[1,2-a]QUINOXALINES*

The reactions of 12 with N-functional groups have been described above. In this section, the reaction of 12 with a carbanion is represented.

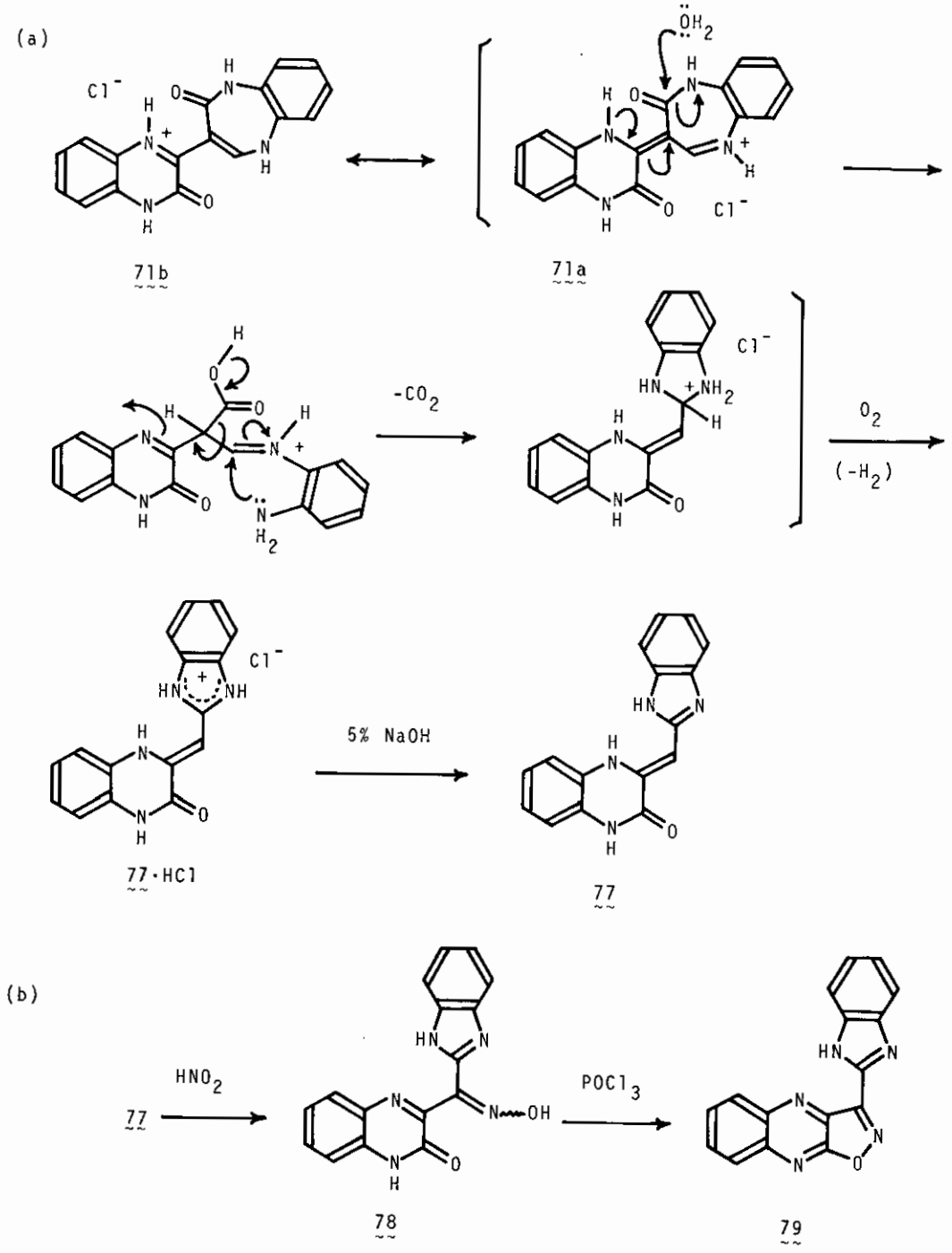
The reaction of 12 with ethyl cyanoacetate in EtONa/EtOH resulted in ring transformation to produce the spiro[2-cyclobutene-1,2'(1H)-quinoxaline] 82 (86%)[35] (Scheme 32).



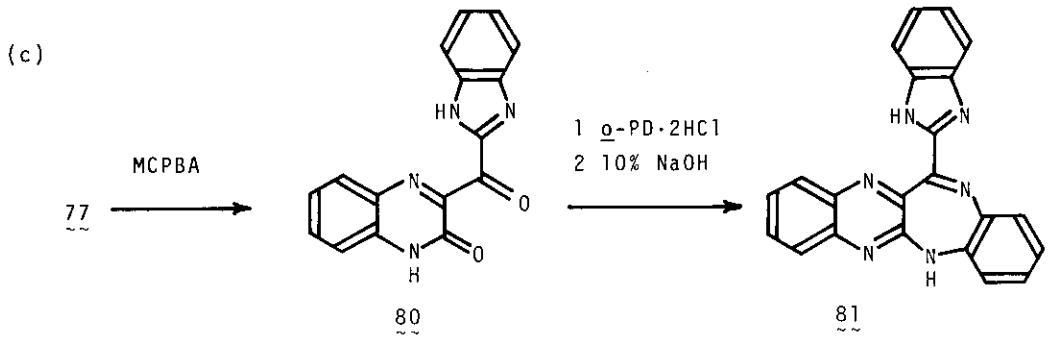
SCHEME 29



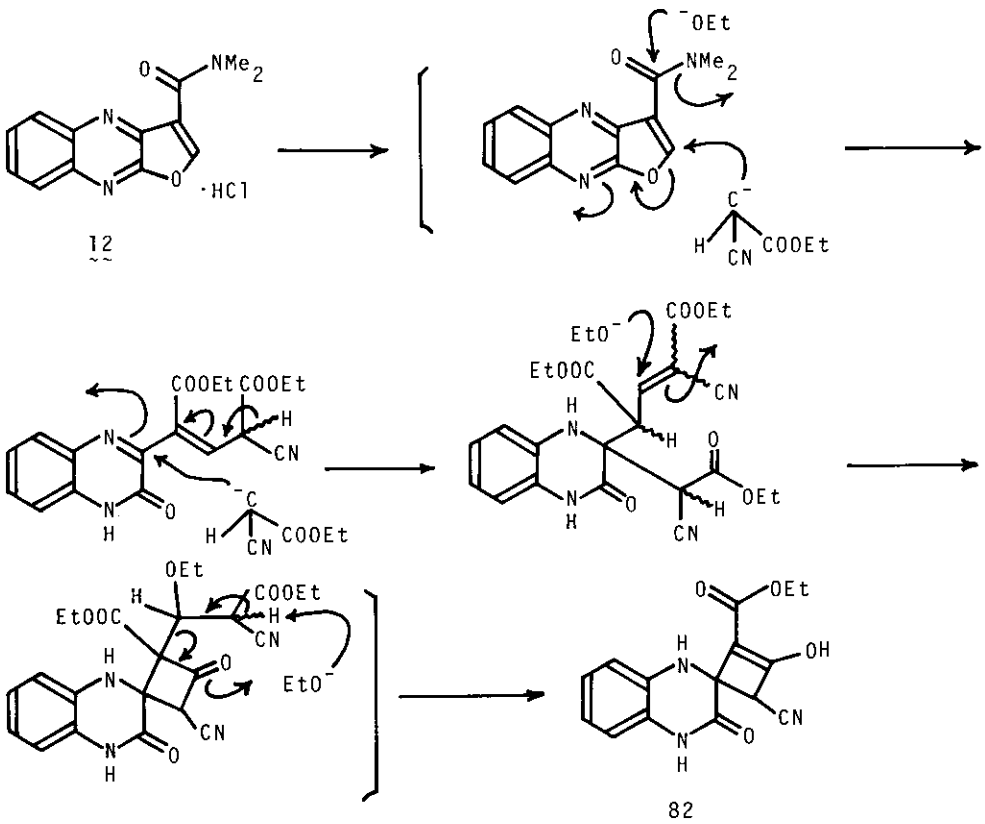
SCHEME 30



SCHEME 31

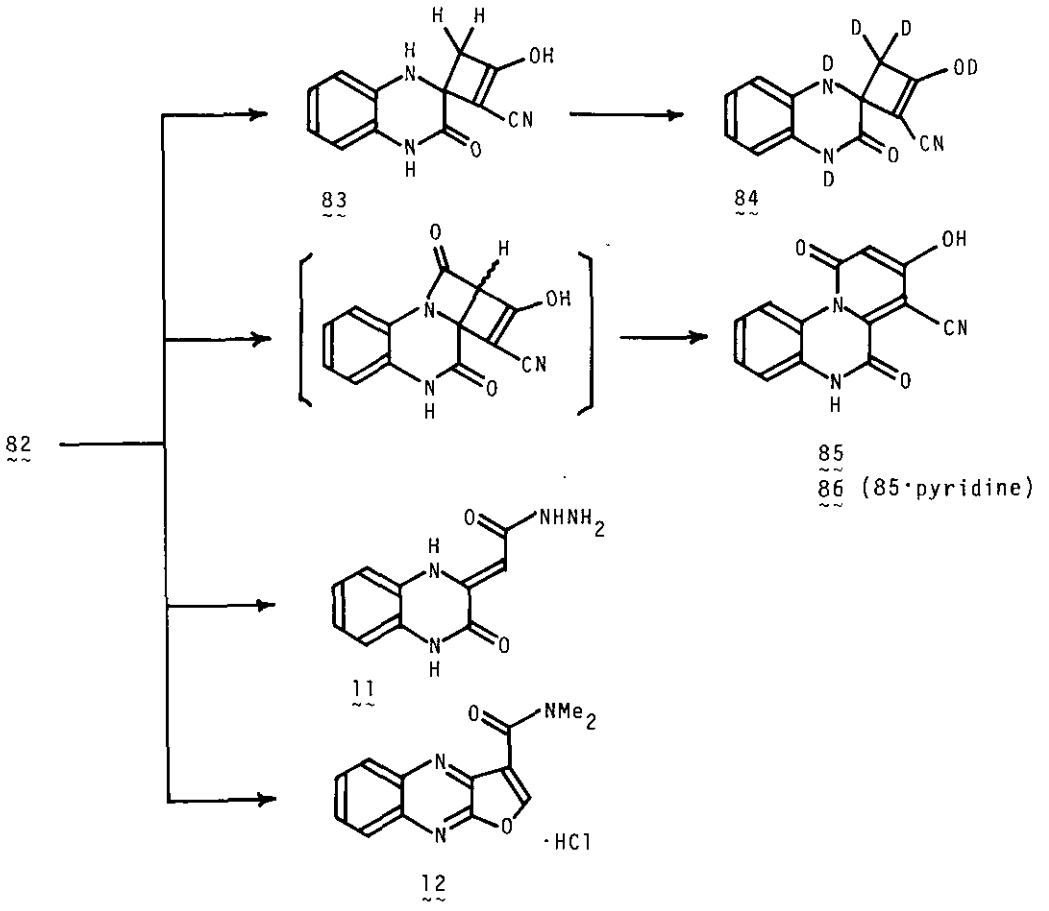


SCHEME 31



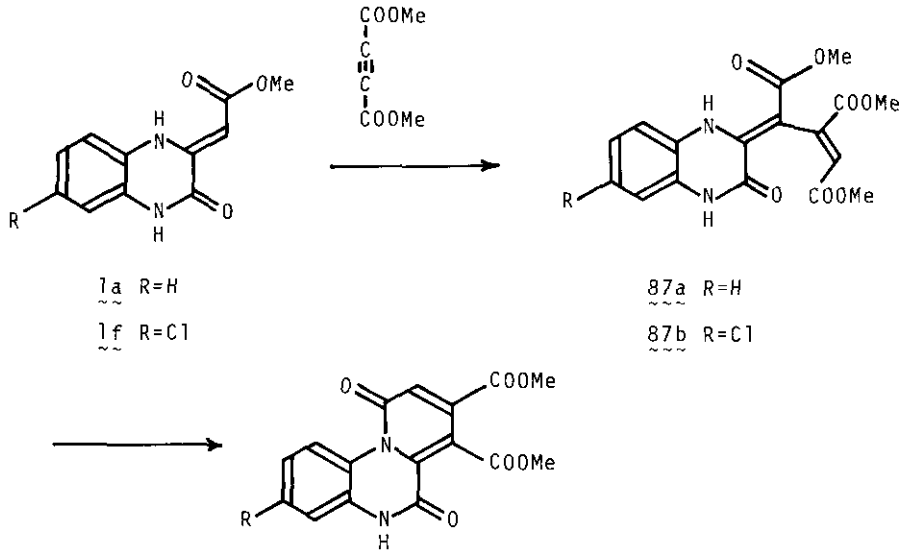
SCHEME 32

Refluxing of 82 in AcOH resulted in hydrolysis and decarboxylation to form an additional spiro[2-cyclobutene-1,2'(1H)-quinoxaline] 83 (93%), whose deuterized species 84 was confirmed on the NMR spectral measurement in D_2O/DMSO-d_6 (Scheme 33). On the other hand, refluxing of 82 in DMF and in pyridine/n-BuOH effected further ring transformation to give the pyrido[1,2-a]quinoxaline 85 (64%) and the pyridinium salt 86 (22%). The reactions of 82 with an excess of hydrazine hydrate and with the Vilsmeier reagent resulted in the formations of the hydrazide 11 (80%) and 12 (56%), respectively.



SCHEME 33

Kawahara et al.[10] also reported the synthesis of the pyrido[1,2-a]quinoxaline ring system (Scheme 34). The reactions of 1a and 1f with dimethyl acetylenedicarboxylate afforded the aconitates 87a (56%) and 87b (20%), respectively, whose refluxing in dry DMSO provided the pyrido[1,2-a]quinoxaline-7,8-dicarboxylates 88a (64%) and 88b (52%), respectively.



1a R=H

1f R=Cl

87a R=H

87b R=Cl

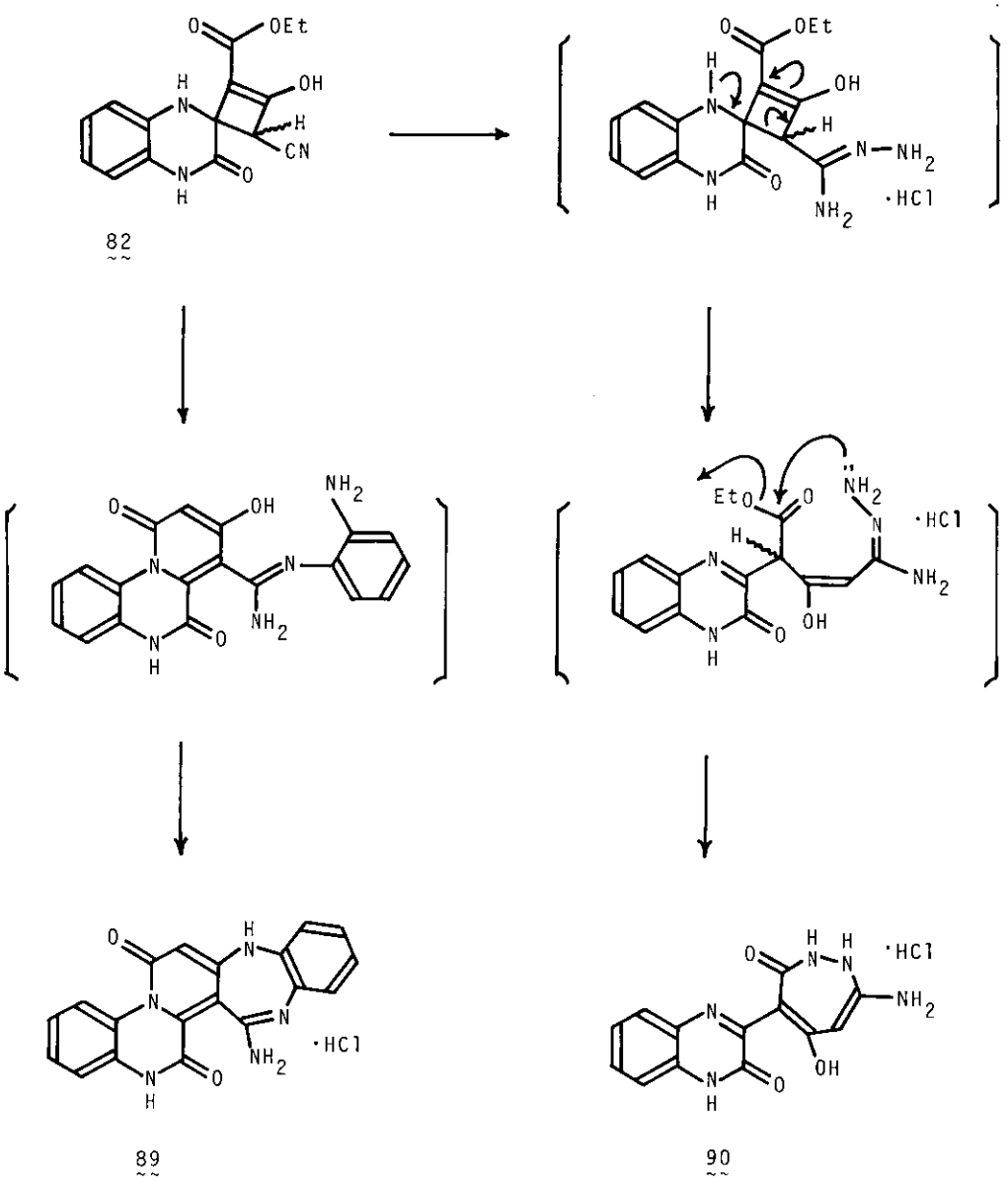
88a R=H

88b R=Cl

SCHEME 34

e. QUINOXALINO[1',2':1,2]PYRIDO[4,3-b][1,5]BENZODIAZEPINE AND QUINOXALINYL-1,2-DIAZEPINE

The reaction of 82 with o-phenylenediamine dihydrochloride (1.5-fold) and hydrazine dihydrochloride (5-fold) in AcOH effected ring transformations to produce the quinoxalino[1',2':1,2]pyrido[4,3-b][1,5]benzodiazepine hydrochloride 89 (44%) and quinoxalinyl-1,2-diazepine hydrochloride 90 (70%), respectively, via intermediates[35,36] shown in Scheme 35.



82

89

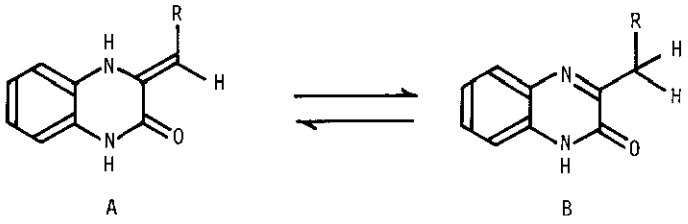
90

SCHEME 35

VI. TAUTOMERIC BEHAVIORS OF 3-HETEROARYLMETHYLENE-2-OXO-1,2,3,4-TETRAHYDROQUINOXALINES

Some of 3-heteroarylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxalines (prepared in the section V-2) exhibited the interesting tautomeric equilibria, which were confirmed by the NMR spectra in DMSO-$\underline{d}_6$ and TFA.[5,6,7]

Compounds 30a,b, 34, 35, 40a,b, and 46a,b exhibited the two tautomers A and B in DMSO-$\underline{d}_6$ (Scheme 36).[37] The tautomer A is predominant in a low temperature, while the ratio of the tautomer B increased in a high temperature.[37] In TFA, 30a, 30b, and 35 represented the three tautomers C, D, and E (Scheme 37), while 34, 40a,b, and 46a,b showed only one species D (Scheme 38). On the other hand, the methylenic C-functionalized compounds 32 (Scheme 39) and 44 (Scheme 40) exhibited the two tautomers (C and E in 32; two of C, E, and G in 44), while 43 represented the one tautomer C or E (Scheme 41).

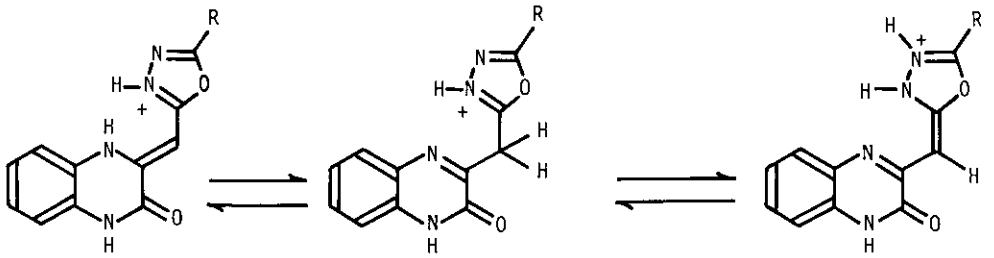


Compound

30a,b 34 35

40a,b 46a,b

SCHEME 36 Equilibria in DMSO-$\underline{d}_6$

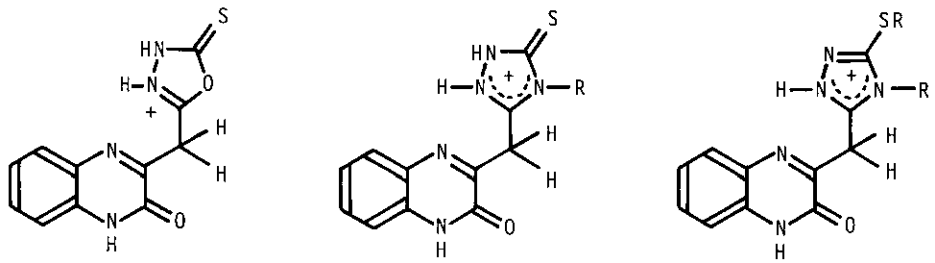


C D E

Compound

30a 30b 35

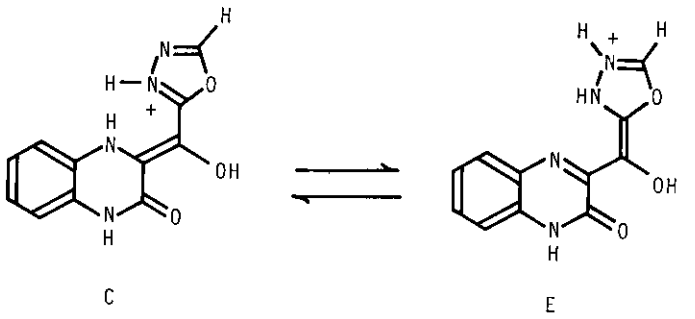
SCHEME 37 Equilibria in TFA



D D D

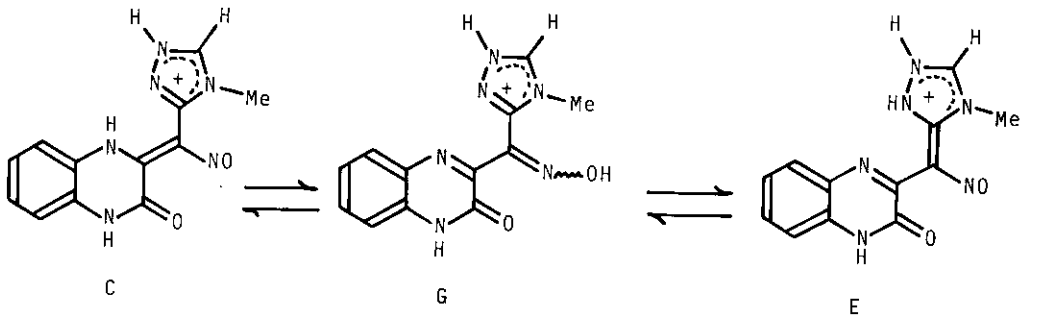
34 40a,b 46a,b

SCHEME 38 Equilibria in TFA



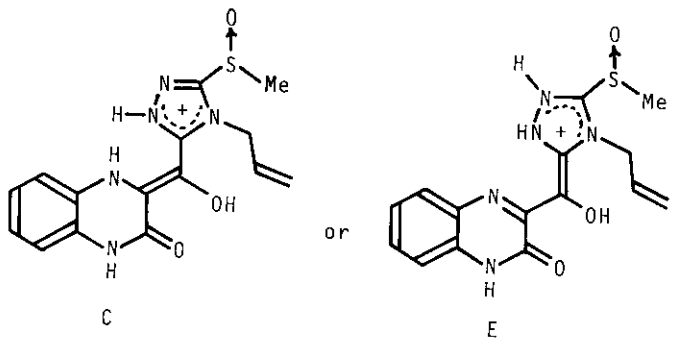
C E

SCHEME 39 Equilibria of 32 in TFA



C G E

SCHEME 40 Equilibria of 44 in TFA



C or E

SCHEME 41 Protonated Species of 43 in TFA

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