3(2*H*)-Pyridazinones: Some Recent Aspects of Synthetic and Medicinal Chemistry

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Introduction.

Among the pyridazine derivatives, 3(2*H*)-pyridazinones form an important class of compounds due mainly to their biological activities and their easy functionalization(s) at various ring positions which also makes them attractive synthetic building blocks for mono- and polycyclic pyridazines. Recently, Coates discussed 3(2*H*)-pyridazinones as a part of his excellent review [1], whereas some interesting chemical and biological aspects of 4,5-disubstituted 3(2*H*)-pyridazinone derivatives were the subjects of our own and Dal Piaz's reviews [2,3]; furthermore, some pharmacologically active pyridazinones also appeared in the comprehensive reviews of Heinisch and Frank [4,5]. In this paper we will describe some recent significant achievments in the synthetic and medicinal chemistry of 3(2*H*)-pyridazinones, focusing on structure-reactivity and structure-biological activity relationships; additionally, some novel pyridazine ring systems obtained from a monocyclic pyridazinone in a multi-step pathway will also be discussed.

We proceed along the following lines:

i) Alkylation of 3(2*H*)-pyridazinones:
Synthesis of GYKI 16 084, a novel drug candidate;

ii) Nucleophilic substitutions at the 4- and 5-positons of 3(2*H*)-pyridazinones: Syntheses of pyridazino[4,5-*b*]-oxazepines, thiazepines, oxazines and diazepines;

iii) Cycloaddition reactions of 3(2*H*)-pyridazinones:
- Diels-Alder reactions,
- Dipolar cycloadditions;

iv) Electrophilic substitution at 4-position of 3(2*H*)-pyridazinones: Syntheses of 4-pyridazinaldehydes, pyrano-[2,3-*d*]pyridazine and pyridazino[4,5-*d*][1,3]oxazine derivatives;

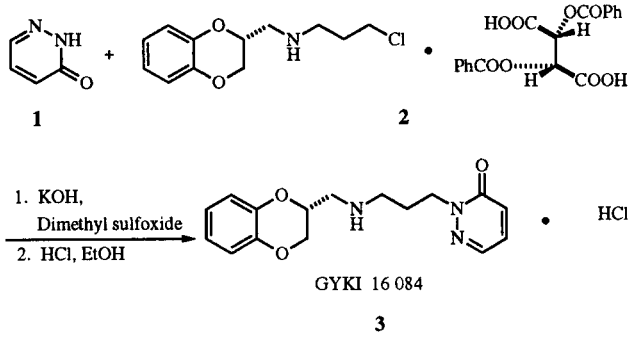
v) *Tertiary*-amino effect: Synthesis of tri- and tetracyclic pyridazinones.

I. Alkylation of 3(2*H*)-pyridazinones.

A variety of substituents could be introduced by treatment of 3(2*H*)-pyridazinones unsubstituted at the 2-position with the appropriate alkylating agent. Alkylation usually affords 2-*N*-substituted derivatives, however, 1-*N* and *O*-alkylations have also been reported in some cases [1,2].

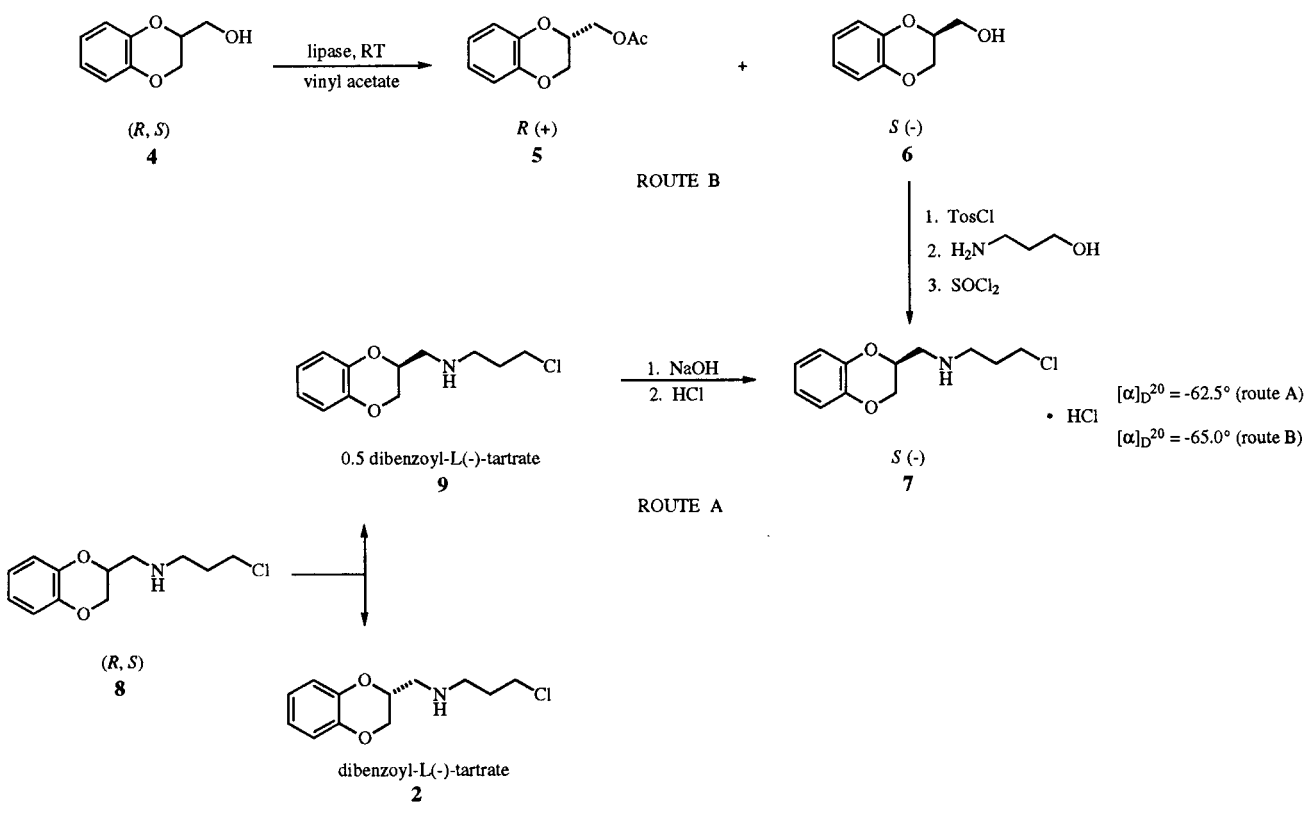
GYKI 16084 (**3**), a ((benzodioxanyl)methylaminopropyl)pyridazinone was obtained in excellent yield by alkylation of the potassium salt of 3(2*H*)-pyridazinone with enantiomerically pure **2** in dimethyl sulfoxide (Scheme 1) [6]. The absolute configuration (designated as *R*) of **3** was proven by chemical correlation (Scheme 2) [7], and CD spectroscopy [8]. Accordingly, the hydrochloride of (*S*)-2-(*N*-(3-chloropropyl)aminomethylbenzo[1,4]dioxane (**7**), the base form of which is in an enantiomeric relationship to the key intermediate **2**, was prepared by independent routes. Resolution of the racemate with dibenzoyl-L-tartaric acid afforded **2** as a dibenzoyltartrate salt, which was converted to the corresponding hydrochloride (route A). In the route B, conversion of (*S*)-2-hydroxymethylbenzo[1,4]dioxane (**6**), available easily by a known enzymatic resolution procedure, into **7** was achieved in three steps (route A). The two products obtained by routes A and B proved to be practically identical (Scheme 2). Further support for the absolute configuration of GYKI 16084 (**3**) was provided by CD measurements. The CD spectrum of compound **3** exhibited an analogous curvature with (*R*)-2-hydroxymethylbenzo-[1,4]dioxane.

Scheme 1



GYKI 16084 (**3**) was found to be a combined α_1- and postsynaptic α_2-adrenoceptor antagonist, which also showed high activity in various *in vitro* and *in vivo* models of benign prostatic hyperplasia. Remarkably, it exerted excellent uroselectivity; this is a very important and valu-

Scheme 2



able feature of this compound, since most drugs marketed for the therapy of benign prostatic hyperplasia until now have their own limitations in this respect. An Investigational New Drug (IND) application for GYKI 16084 has recently been filed in Hungary.

Some structurally relating pyridazinones were also blockers of the α-adrenoceptors [9,10] but no information has been published about their activity in benign prostatic hyperplasia models.

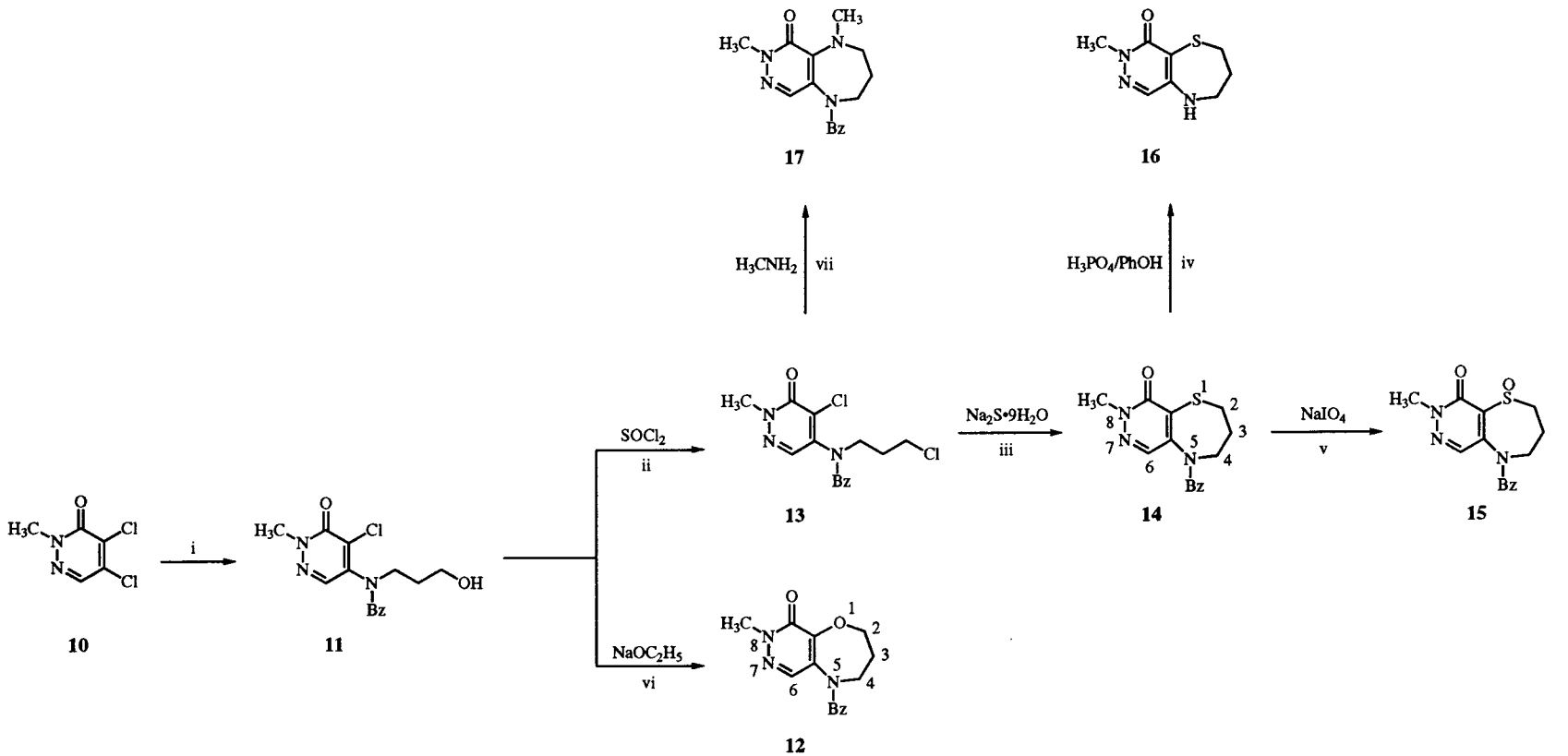
II. Nucleophilic Substitutions at the 4- and 5-Positons of 3(2*H*)-Pyridazinones: Synthesis of Pyridazino[4,5-*b*]-oxazepines, Thiazepines, Oxazines and Diazepines.

4,5-Dihalo-3(2*H*)-pyridazinones have attracted much attention as valuable starting materials for mono- and polycyclic pyridazines [2]. Particularly, nucleophilic displacements of halo atoms at the 4- and 5-positions may provide a simple and efficient way for preparation of 4,5-(or *d*-) fused pyridazines. In these reactions, generally a normal addition-elimination mechanism operates with *ipso* substitution [11], although an aryne type mechanism [12] has also been reported.

Interestingly, in nucleophilic reactions of structurally relating 5-bromo-3,6-pyridazindiones, *cine* and *ipso* [13], and even vicarious substitutions [14] have also been described. In the reaction of 4-cyano-3(2*H*)-pyridazinone with phenylmagnesium chloride, an unusual *ipso* attack was also detected [15].

Pyridazinones possessing a halo and an *ortho*-hydroxyalkylamino or -chloroalkylamino substituent may easily undergo intramolecular nucleophilic reactions to afford bicyclic compounds. In this way, pyridazino[4,5-*b*]-[1,5]oxazepine **12**, pyridazino[4,5-*b*][1,5]thiazepines **14** as well as a pyridazino[4,5-*b*][1,5]diazepine **17** have been prepared starting from 4,5-dichloro-2-methyl-3(2*H*)-pyridazinone (**10**) (Scheme 3). All these ring systems are of great interests as ring closed analogues of pharmacologically active monocyclic pyridazinones [16,17] and/or as promising pharmacophores *per se*. A convenient synthetic route was also developed to 5-aminoacyl and 5-aminoalkylpyridazinooxazepines and -thiazepines **21-24** (Scheme 4) [18]. Of these compounds, several 5-aminoacyl derivatives of general formulae **21** and **22** showed moderate to high affinities for serotonine (5-HT)-1A-receptors without exerting comparable affinities for other G-protein coupled receptors. On the basis of *in vivo* experiments, one compound (in formula **21**, n:2, R^1, R^2: H, R^3: 2-methoxyphenoxyethylamino) has been selected

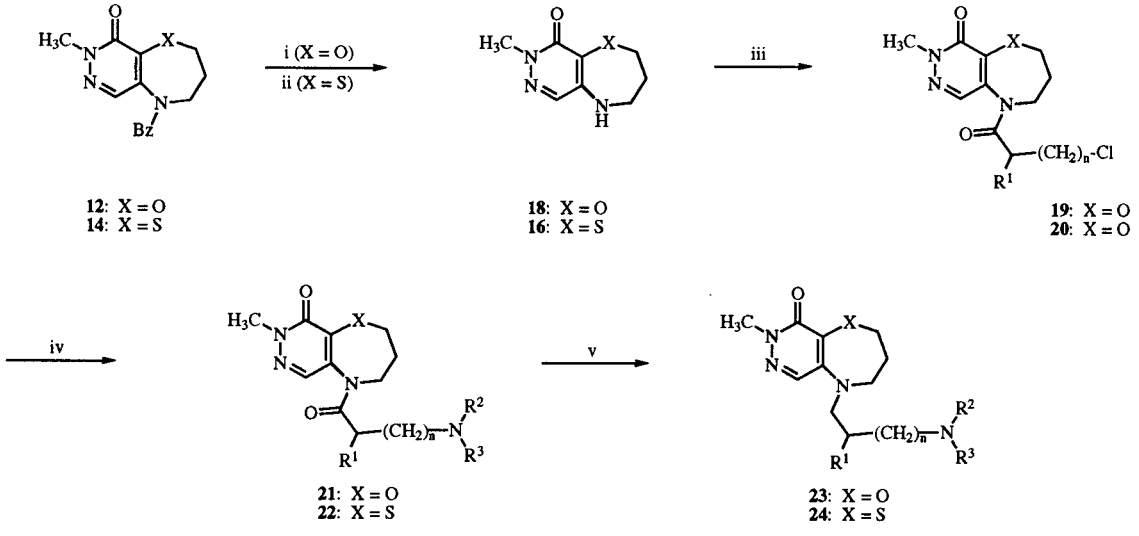
Scheme 3



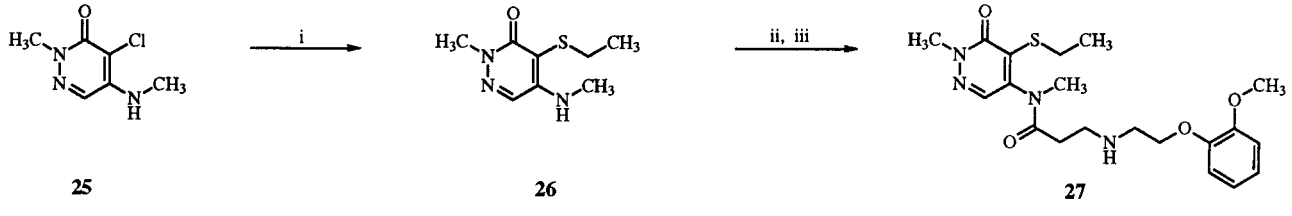
i: $BzNH(CH_2)_3OH$, H_2O, reflux; ii: CH_2Cl_2, reflux; iii: CH_3OH-H_2O, reflux; iv: 150°, 3 hours; v: AcOH-H_2O, 0°, 2 hours; vi: C_2H_5OH, reflux, 6 hours; vii: C_2H_5OH, 120°, 3 hours.

for preclinical development as a promising anxiolytic drug candidate. It is also noteworthy that the 5-aminoalkyl derivatives **23**, **24** were less active, whereas the acyclic thiazepine analogue **27** exhibited a fairly high affinity for the serotonine-1A receptors. A quantitative model for structure - serotonine-1A affinity relationships was also developed by a comparative molecular field analysis [19].

Scheme 4



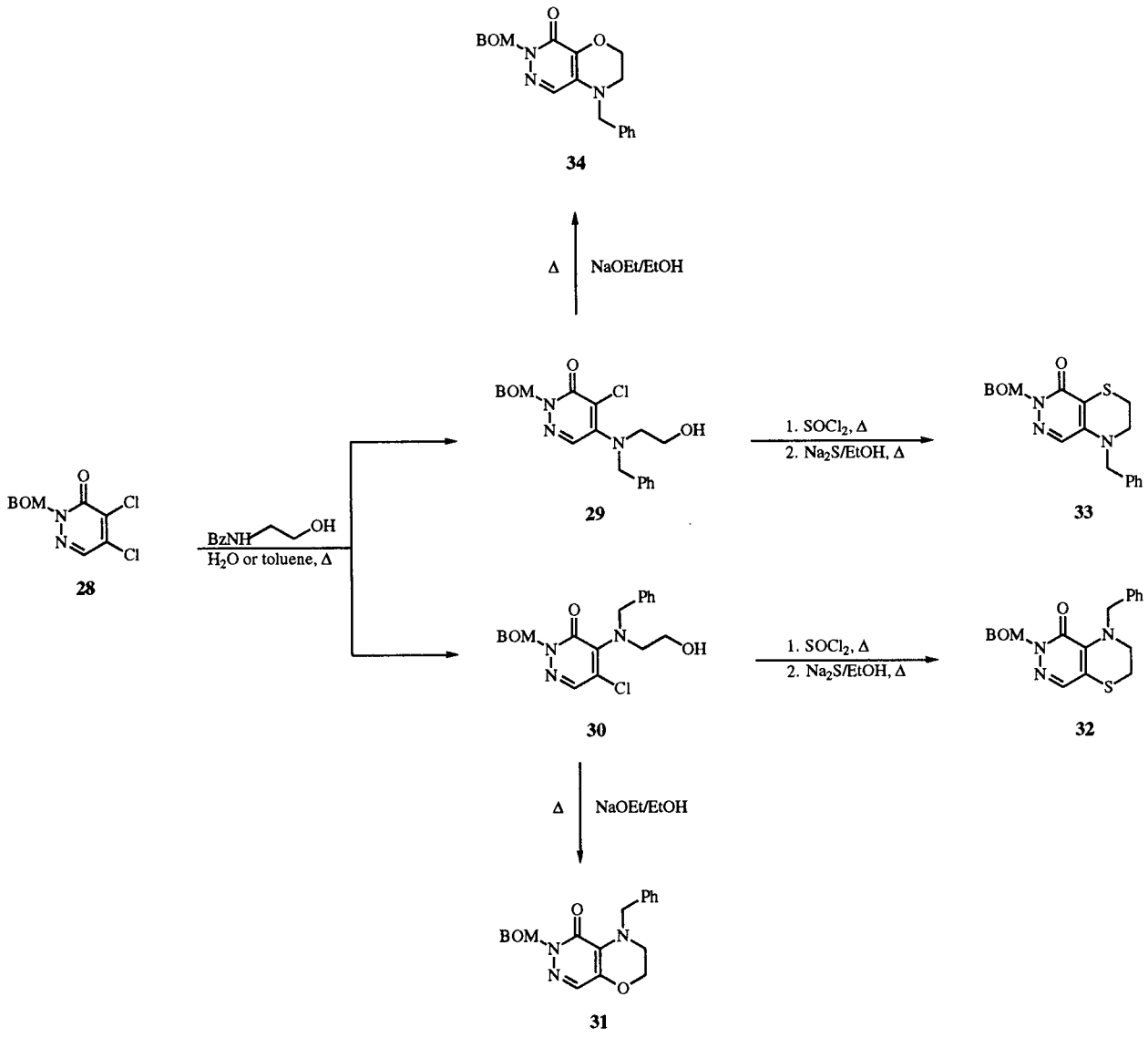
i: Pd/C, cyclohexene, EtOH, reflux, 1 hour; ii: PhOH, H_3PO_3, 150°, 3 hours; iii: $Cl(CH_2)_nCH(R^1)COCl$, CH_3CN, Et_3N, or 4-(dimethylamino)pyridine, 40-45°, 4 hours; iv: R^2R^3NH, 3 hours, v: tetrahydrofuran, B_2H_6, rt, 6 hours.



i: NaH, EtSH, PhH, reflux 22 hours; ii: $Cl(CH_2)_2COCl$, dimethylformamide, 4-(dimethylamino)pyridine, 45-50°, 2 hours; iii: *o*-methoxyphenoxyethylamine, 4-(dimethylamino)pyridine, Et_3N, *i*-PrOH, 60°, 2 hours.

For economic functionalizations at the lactam and/or amine nitrogens of pyridazino[4,5-*b*][1,4]oxazines and relating bicyclic ring systems, a powerful combination of protecting groups was elaborated. Thus, for amino nitrogen, benzyl protecting group, for the lactam nitrogen, benzyloxymethyl group could be efficiently used; this combination was first applied for pyridazinooxazines and -thiazines **31-34** (Scheme 5) [20]. These protecting groups could be optionally removed fully selectively or simultaneously, as examplified by preparation of **35-38** from **34** in good yields (Scheme 6). On prolonging the reaction time of catalytic hydrogenation, fairly unexpectedly, the 4-methyl derivative **37** was isolated. The reaction sequence depicted on Scheme 7 may be a plausible mechanism for the formation of **37**. Accordingly, rearrangement of the primarily formed 7-hydroxymethyl intermediate to the 4-hydroxymethyl derivative followed by reduction affords **37**. (Another possible formation of **37** from the 7-methyl derivative **39** *via* a methyl migration could be unambiguously excluded).

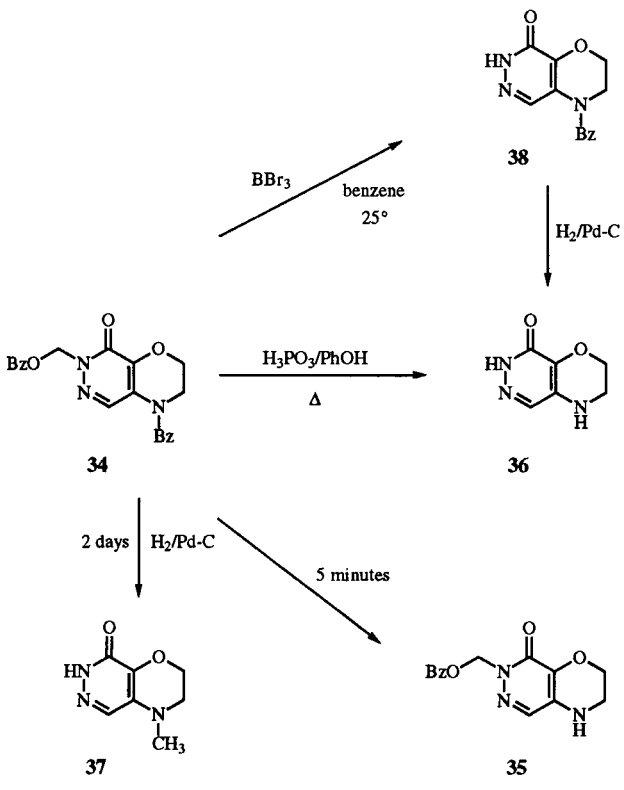
Scheme 5



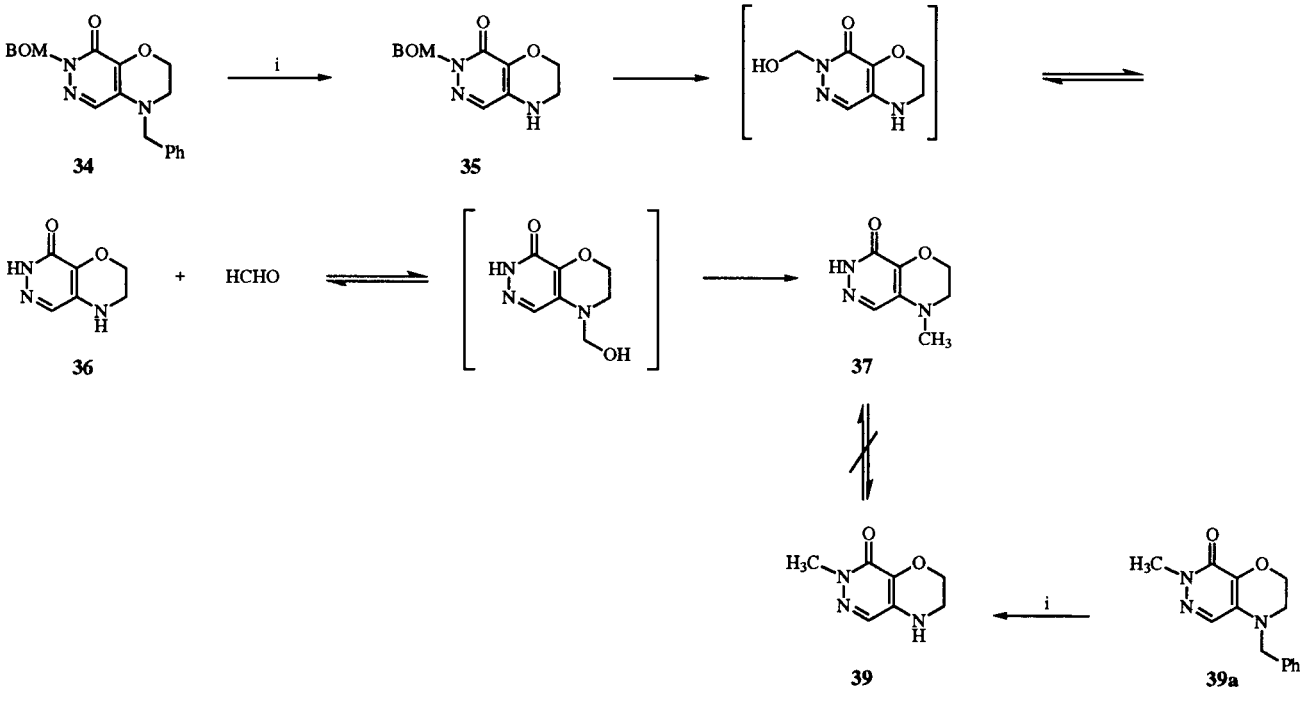
Applying the same protecting/deprotecting strategy to the pyridazinothiazepine **40**, some novel otherwise hardly accessible derivatives were easily obtained (Scheme 8). Removing the benzyloxymethyl group gave **41**. Compounds **44** were prepared in two steps from the latter compound. First alkylation with epichlorohydrin was carried out, and subsequently the epoxide thus formed was reacted with amines. In a one-pot procedure, the chloro derivative **42** was obtained from **40** with phosphoryl chloride in 40% yield. Compound **42** could be smoothly converted to the hydroxyethylamino derivative **43** in 60% yield.

The conveniently available 4,5-dichloro-2-methyl-6-nitro-3(2*H*)-pyridazinone (**45**) and its *N*-ribofurasonyl analogue have also been used for preparation of bicyclic ring systems [2,21]. We also studied the transformations of **45**. It was found that, due to the presence of the nitro group, a substantial change might occur in the regiochemistry of inter- and intramolecular nucleophilic reactions [2,11,22]. Reaction of **45** with benzylaminopropanol in ethanol gave the 5- and 4-isomers **46** and **47** in 45% and 35% yields, respectively; ^{13}C nmr shifts are of diagnostic value in structural assignments (Scheme 9) [23]. Ring closure reaction of **46** followed a different pattern as

Scheme 6

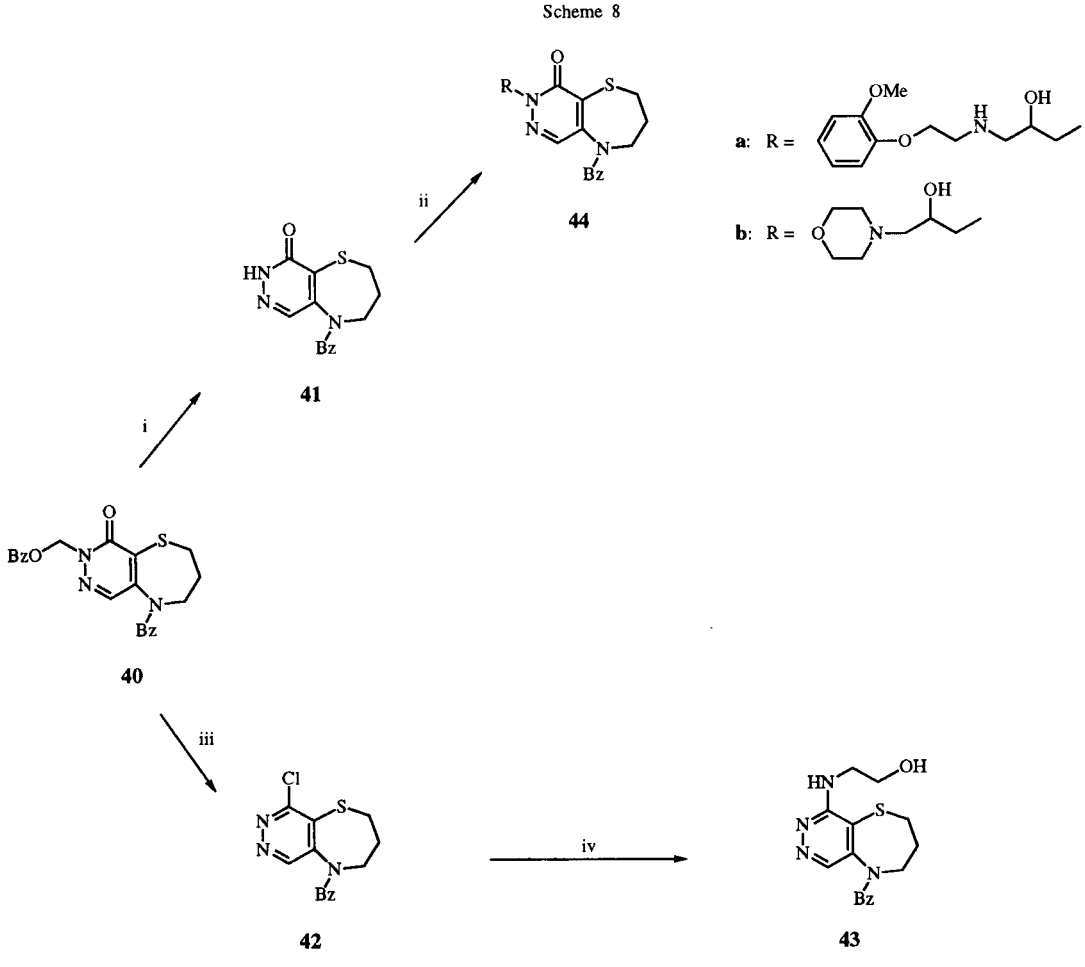


Scheme 7



i: H_2/Pd-C/MeOH/H^+, rt.

Scheme 8

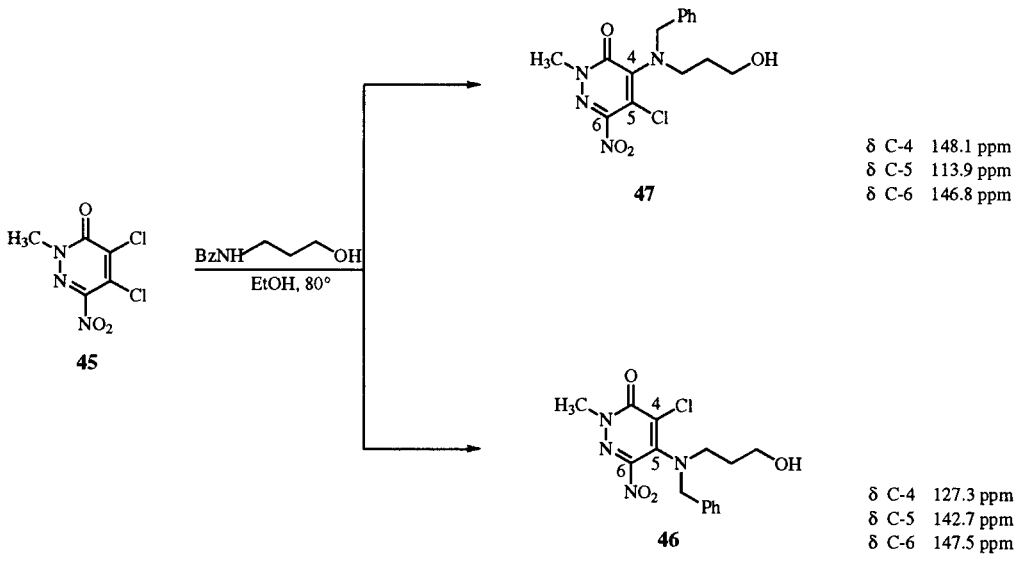


i: BBr_3/toluene, 25°; ii: 1. NaOEt/EtOH, 25°, 2. epichlorohydrine/dimethyl sulfoxide, 25°; 3. R^1R^2NH, reflux; iii: $POCl_3$, reflux; iv: $H_2N(CH_2)_2OH$, 130°.

expected from the behavior of denitro analogues **11**. Treatment of **46** with sodium ethoxide afforded the pyridazino[3,4-*b*][1,5]oxazepine **52** as main product (55%), and, as a minor product, the pyridazino[4,5-*b*][1,5]oxazepin-6-one **48** (15%) could also be isolated; in contrast, formation of the isomeric pyridazino[4,5-*b*][1,5]oxazepin-9-one **51**, which is the nitro analogue of **12**, could not be detected (Scheme 10). Formation of the 6-one derivative **48** in this reaction could be explained by a Smiles rearrangement. In the first step, the hydroxyl group of **46** attacks at C-5, rather than at the C-4 atom as a consequence of the strong elctron-withdrawing properties of the neighboring nitro group, and then ring opening of the intermediate and subsequent formation of the oxazepine ring with the involvement of C-4 and the amino nitrogen may lead to **48**. (Although, Smiles rearrangement of pyridazinyl amino alcohols has not been reported, a mechanistically similar transformation of a pyridazine derivative has recently been described [23]).

Spectroscopic data fully supported the structure of **48**. Thus, *e.g.*, the ^{13}C nmr signal of C-5a in **48** was shifted upfield to that of **52** (132.5 and 146.7 ppm, respectively). For unequivocal structural identification, compound **48** was also synthesized by ring closure of **47**.

Scheme 9



Additional support for the structure of the [3,4-*b*] annelated **52** was given by a synthetic transformation and ^{1}H nmr measurements. From **52**, compound **53** was prepared *via* catalytic dehalohydrogenation; in this compound, the benzylic methylene and the 6-CH proton signals gave a positive NOE.

Each nitro derivative could be smoothly transformed into the corresponding amino compound under Béchamp conditions in moderate to good yields. Interestingly, of the two isomeric hydroxypropylamino derivatives **50** and **54**, the 5-isomer **54** could only be cyclized by treatment with sodium ethoxide to the corresponding oxazepine **56**; on the other hand, in the case of **50**, the electron donor 6-amino substituent prevented the nucleophilic attack at the 5-position.

Cyclization of the amino derivative **56** with triethyl orthoformate or diethyl pyrocarbonate gave **57** and **58** which are the first representatives of the *peri*-fused 2,3,4,9a-tetrazabenzo[*c*,*d*]azulene ring system [23].

Angularly fused tricyclic derivatives have also been prepared from the dichloropyridazinone **10**.

Syntheses of two tricyclic pyridazino[4,5-*b*]oxazines **62**, **63** and the piperidino fused pyridazino[4,5-*b*]oxazepine **64** have been accomplished by utilizing the ring closure reactions of *ortho*-chloro hydroxyalkylamino derivatives. The intermediates **59-61** could be easily obtained from the appropriate cyclic aminoethanols (Scheme 11). The pyrrolo fused derivatives **59** and **62** were also prepared in enantiomerically pure forms [24,25].

Synthesis of the pyrrolo fused pyridazino[4,5-*b*]thiazepine ring system was however achieved in a conceptually different route. In the key step of this synthesis, compound **65**, prepared from dichloropyridazinone **10** in four steps [26], was cyclized into **66** by a C-alkylation in 31% yield (Scheme 12).

III. Cycloaddition Reactions of 3(2*H*)-Pyridazinones.

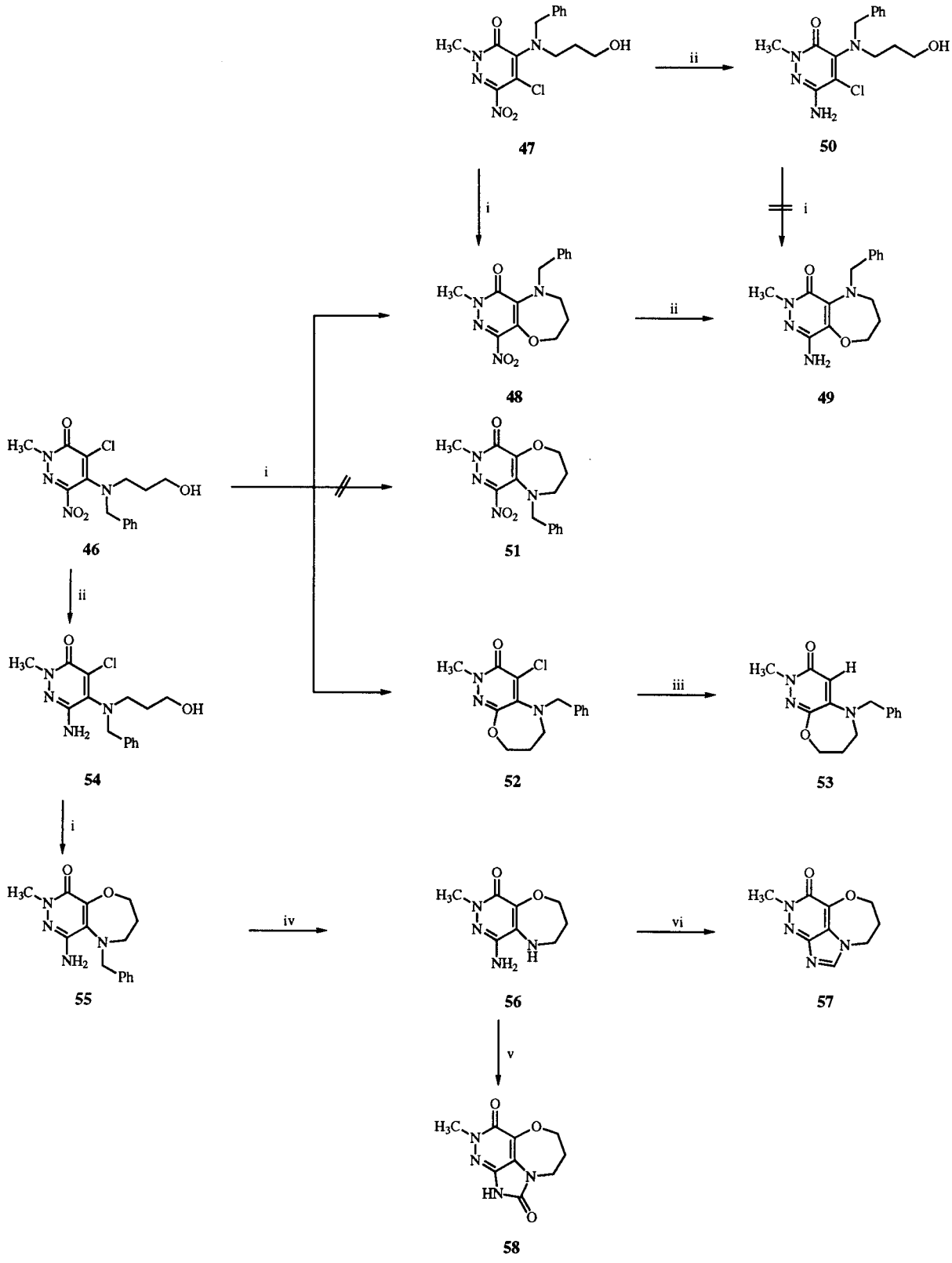
A. Diels-Alder Reactions.

Pyridazines have been shown to undergo Diels-Alder reactions as dienes with inverse electron demand, and the versatility of this methodology has been well demonstrated by many examples including preparations of polycyclic pyridazines [27]. On the other hand, a few precedent Diels-Alder reactions have been reported, in which a pyridazine served as a dienophile. We chose 5-iodo- and 5-ethylsulfonyl-2-methyl-3(2*H*)-pyridazinones **67a,b** as possible dienophiles in Diels-Alder reactions with normal electron demand on the basis of semiempirical quantum chemical calculations (both compounds have a low-lying HOMO (Figure 1)); moreover, compounds **67a** and **67b** also possess a good leaving group at the predicted site of cycloaddition, the presence of which was expected to make the full reaction pathway irreversible. Indeed, reaction of **67a** and **67b** with dimethylbutadiene afforded the dihydrophthalazinone **68** that could be easily aromatized to **69** [28] (Scheme 13). Dal Piaz and Farina also described other interesting examples of using pyridazinones, such as **71** and **67b**, respectively, as dienophiles [29,30] (Scheme 14).

B. Dipolar Cycloadditions.

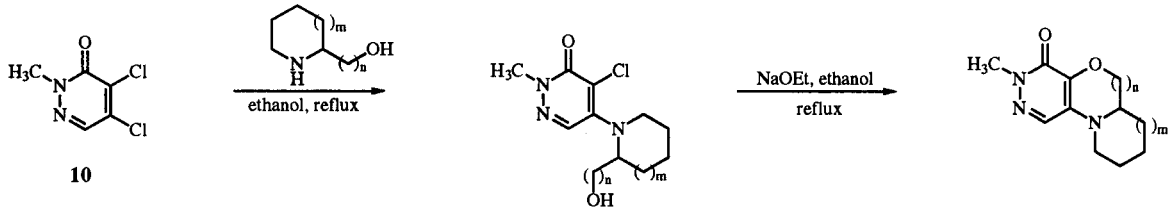
Systematic studies of 1,3-dipolar cycloaddition reactions of 3(2*H*)-pyridazinones have been published in recent years. In particular, Stanovnik thoroughly reviewed

Scheme 10



i: NaOEt/EtOH, reflux, 1 hour; ii: Fe/AcOH, rt, 2 hours; iii: $HCOONH_4$/EtOH/Pd(C), reflux, 1 hour; iv: cyclohexene/EtOH/Pd(C), reflux, 1 hour; v: $(EtOOC)_2O/CH_2Cl_2$, 40°, 30 hours; vi: $HC(OEt)_3$/EtOH, reflux 4 hours.

Scheme 11

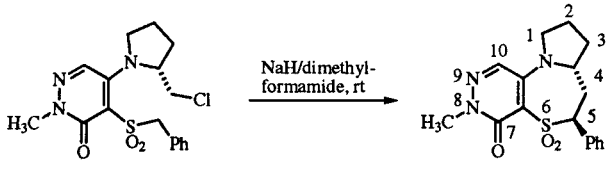


10

59 m = 0; n = 1
60 m = 1; n = 1
61 m = 1; n = 2

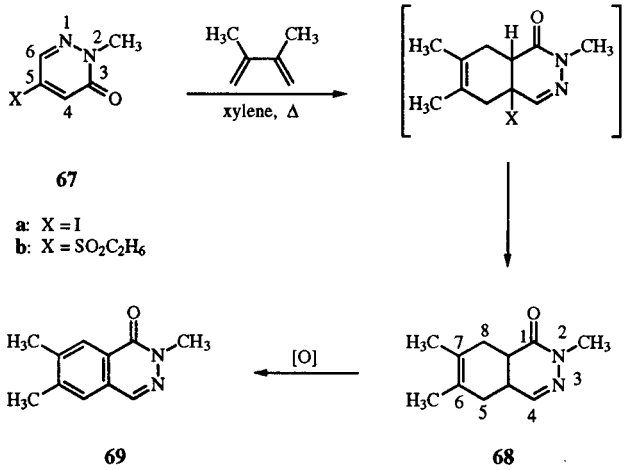
62 m = 0; n = 1
63 m = 1; n = 1
64 m = 1; n = 2

Scheme 12



65 **66**

Scheme 13



67

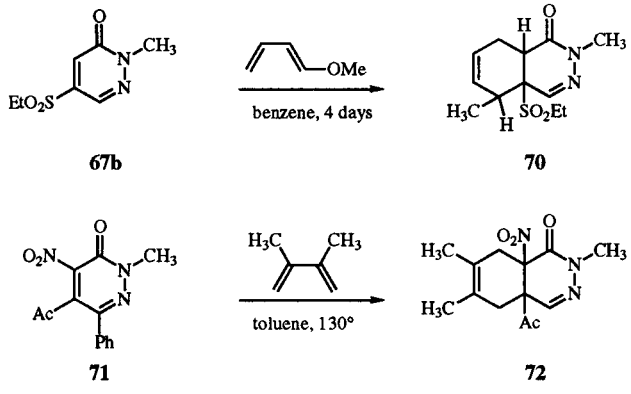
a: X = I
b: X = $SO_2C_2H_6$

69 **68**

	HOMO	LUMO
67b	-9.82	-1.49
10	-9.58	-1.06
67a	-9.60	-0.89
67d	-9.37	-0.48
67c	-8.91	-0.12

Figure 1. The highest occupied and lowest unoccupied orbital (HOMO and LUMO, respectively) energies (eV) of 3(2*H*)-pyridazinone derivatives.

Scheme 14



67b 70

71 72

the reactions of pyridazines with diazoalkanes [31,32] and nitrile oxides [32]. These reactions have been important routes for the syntheses of pyrazolo- and isoxazolopyridazines. A series of nitrile imines prepared *in situ* from α-chlorohydrazones was also shown to undergo cycloaddition reactions with 4,5-unsubstituted 3(2*H*)-pyridazinones affording pyrazolo[3,4-*d*]pyridazines [32].

We also found that the nitrile imine obtained from benzaldehyde phenylhydrazone with chloramine-T [33] smoothly added to the 4,5-double bond of 5-ethylsulfonyl-2-methyl-3(2*H*)-pyridazinone (**67b**) to form the pyrazolopyridazine derivative **73** (Scheme 15). We believe that in this and analogous reactions, the 5-substituent may play a decisive role in the regiochemistry of the cycloaddition.

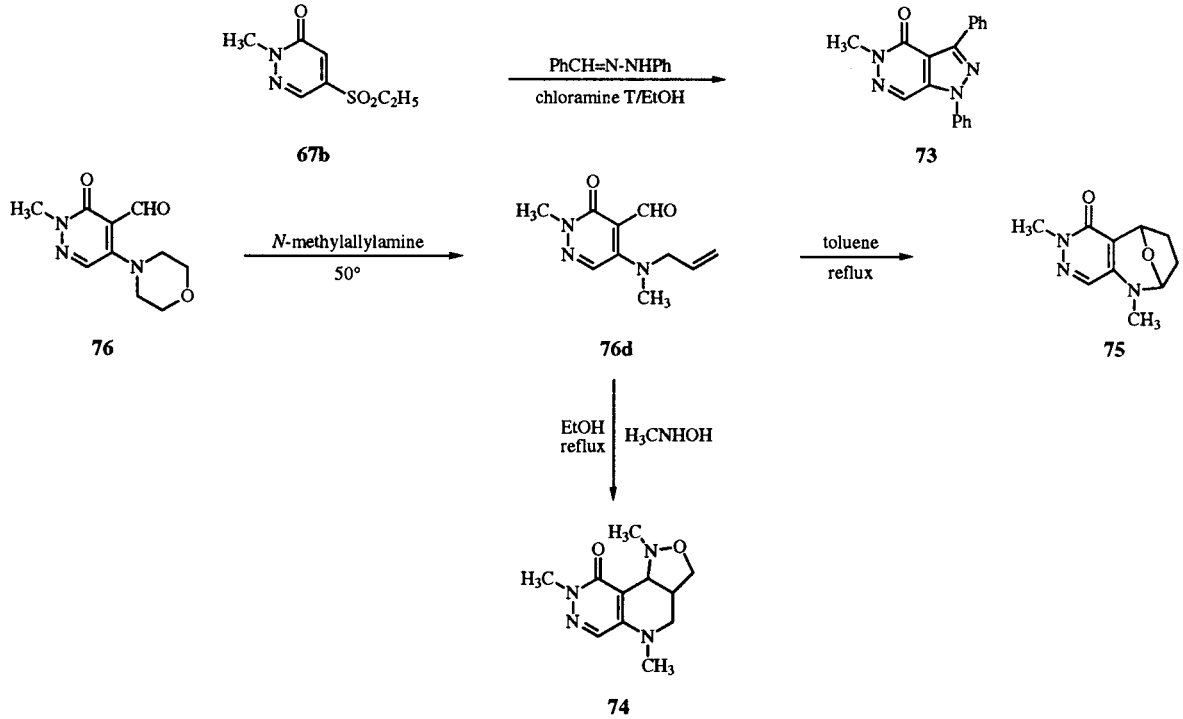
Intramolecular 1,3-dipolar cycloadditions of pyridazinones, to the best of our knowledge, have not been reported earlier. We prepared compound **74**, the first representative of a novel tricyclic isoxazolopyridopyridazine ring system in such a way (Scheme 15) [34]. When compound **76d** was treated with *N*-methylhydroxylamine, an intramolecular addition reaction took place with the involvement of the allylic double bond and the nitrile oxide moiety formed *in situ* from the formyl group with *N*-methylhydroxylamine. The value of the coupling constant of the bridgehead protons (J = 5.5 Hz) suggests a *cis* ring fusion.

Interestingly enough, compound **76d** may also be transformed into another novel ring system by an intramolecular ene-reaction followed by a nucleophilic reaction between the hydroxy group and the C-2 atom of the pyridazinoazepine intermediate thus formed. The bridged compound, 4,8-dimethyl-13-oxa-4,5,8-triazatricyclo[7.3.1.$0^{2,7}$]-trideca-2(7),5-dien-3-one (**75**) was isolated in 40% yield [34].

IV. Electrophilic Substitution Reaction at the 4-Position of 3(2*H*)-Pyridazinones: Syntheses of 4-Pyridazinaldehydes, and Pyrano[2,3-*d*]pyridazine and Pyridazino[4,5-*d*]-[1,3]oxazine Derivatives.

The Vilsmeier reaction is an efficient procedure to introduce a formyl group into a carbo- or heteroaromatic ring activated by electron-releasing groups. As could be expected from the HOMO values of monocyclic pyridazi-

Scheme 15



67b 73

76 76d 75

74

nones shown on Figure 1, 3(2*H*)-pyridazinones possessing a secondary amino group at the 5-position might undergo the formylation reactions to afford the corresponding 4-formyl derivatives. In fact, the 4-formyl derivative of **67e**, *i.e.* compound **76a**, could be smoothly prepared by Vilsmeier formylation [35]. Regiochemistry of the formylation reaction was proven by nmr spectroscopy. Both ^1H and ^{13}C chemical shifts fully supported that formylation was directed to the 4-position of the pyridazinone ring (Figure 2). 5-Hydrazinopyridazines have also been shown to react with the Vilsmeier reagent to give pyrazolopyridazines by formation of the formyl derivatives [36]. This regiochemical outcome of electrophilic substitution can also be well understood by the FMO theory.

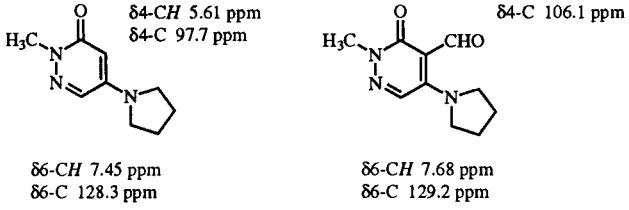
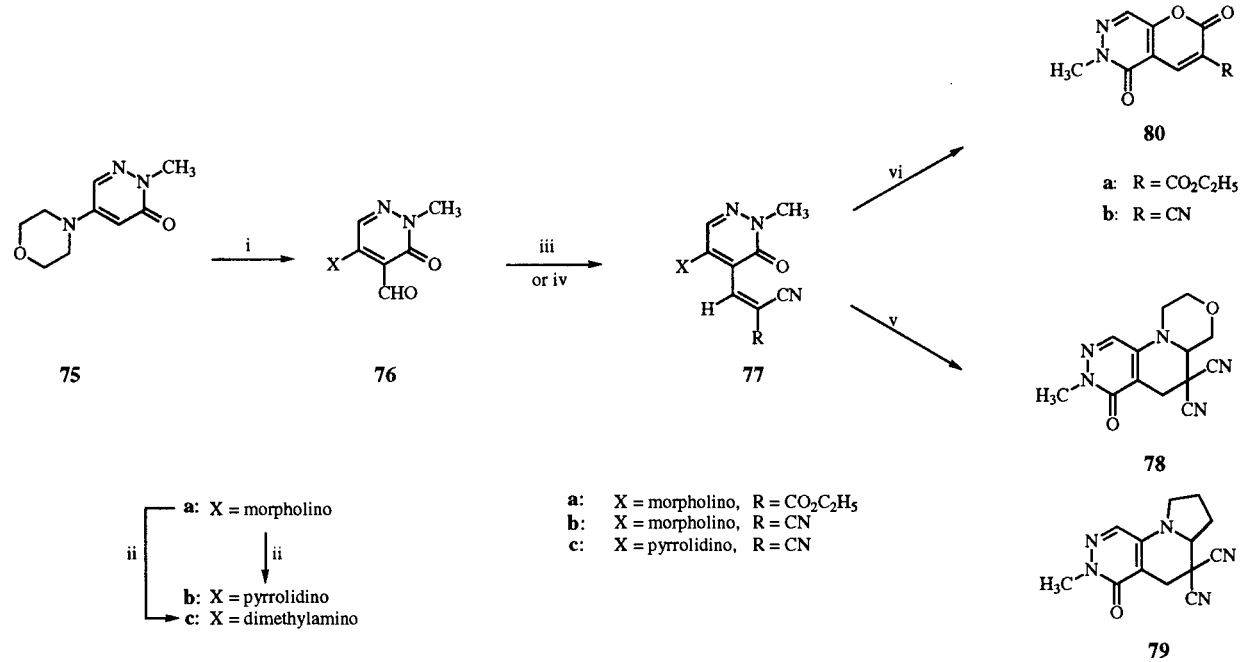


Figure 2. ^1H and ^{13}C nmr shifts of 6-C*H*, 4-C*H*, 6-C and 4-C signals of 5-pyrrolidino-3(2*H*)-pyridazinone and 4-formyl-5-pyrrolidino-3(2*H*)-pyridazinone, respectively.

The morpholino group of 4-formyl-5-morpholino-3(2*H*)-pyridazinone (**76a**) could be exchanged with other secondary amino groups by reactions with the corresponding amines at elevated temperatures. Compounds **76b**, **76c**, **84** and **88** were obtained generally in good yields. All formyl derivatives have been found to be valuable starting materials for preparing 4,5-fused pyridazines.

An extremely efficient tandem methodology was applied for the synthesis of pyranopyridazine derivatives (Scheme 16). The starting materials **77a**, **77b** were prepared from the aldehyde **76a** with ethyl cyanoacetate and malononitrile, respectively, under Knoevenagel conditions. Treatment of **77a** and **77b** with hydrochloric acid afforded the bicyclic compounds **80a** and **80b** in good yields [35].

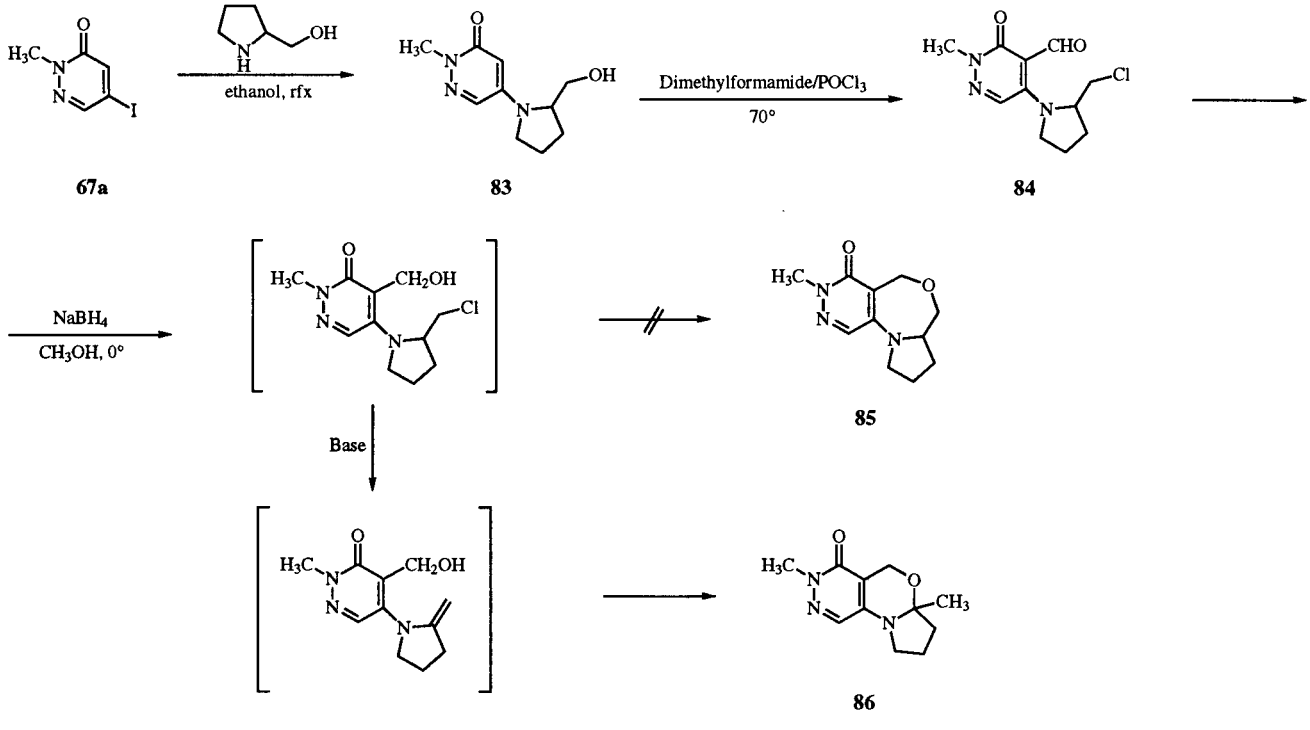
Scheme 16



i: $POCl_3$/dimethylformamide, 70°, 1 hour; ii: R_2NH (excess), rt, 1 day; iii: $CNCH_2CO_2C_2H_5$, C_2H_5OH-pyrrolidine-AcOH, rt, 1 day; iv: $(CN)_2CH_2$, C_2H_5OH, rt, 3 days; v: dimethyl sulfoxide, 150°, vi: 2-4*N* HCl, rt.

The aldehyde **84** possessing a chloromethyl side chain at the pyrrolidino ring, had also been considered as a valuable building block for the synthesis of a novel tricyclic ring system. However, when treated with an excess of sodium borohydride in methanol, **86**, a pyridazinooxazine derivative with a 6,6,5 ring combination, was isolated instead of the expected pyridazinooxazepine derivative **85** (Scheme 17). Formation of **86** might proceed *via* an intermediate obtained by elimination of hydrogen chloride. A subsequent nucleophilic addition could lead to the tricyclic product [37].

Scheme 17



67a **83** **84** **85** **86**

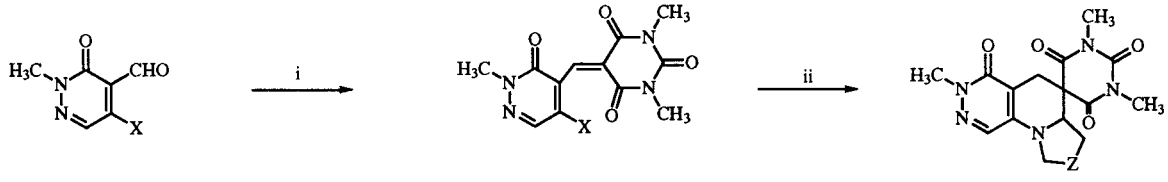
V. Tertiary Amino Effect: Syntheses of Tri- and Tetracyclic Pyridazinones.

The versatility of the *tert*-amino effect was recently well demonstrated by the excellent review of Meth-Cohn [38]. This methodology was first applied by us to the synthesis of polycylic pyridazines [35]. It was found that pyridazinones containing a sufficiently electron poor vinylic bond and an *ortho-tert*-amino group could undergo cyclization. In particular, dinitriles such as compounds **77b** and **77c** could be transformed into the pyridazino[4,5-*e*]indolizine-6,6-dicarbonitrile **78** and the pyridazino[5'4':5,6]pyrido[2,1-*c*][1,4]oxazine-6,6-dicarbonitrile derivative **79** (Scheme 16).

An interesting synthetic aspect of the *tert*-amino effect has more recently been realized. For preparation of two novel spirocyclic ring systems represented by **82a** and **82b**, cyclization reactions of the corresponding Knoevenagel products **81a** and **81b**, respectively, were carried out. These reactions took place smoothly to afford the spiropyrimidine derivatives in 70% and 71% yields (Scheme 18) [34]. It is also noteworthy that the tetracyclic compounds **82** could be formed at a much lower temperature than it was required for the formation of tricyclic analogues **78** and **79**. Presumably, this may be attributed to differences in the geometric features of the respective transition states. If so, an enhanced cyclization tendency by the *tertiary*-amino effect may generally be expected for compounds in

which one atom of the vinylic group is incorporated into an electron deficient ring. Therefore, the *tertiary*-amino effect may also offer a novel, convenient and powerful approach for the synthesis of complex spirocyclic systems.

Scheme 18



76a,b **81** **82**

a: X = morpholino
b: pyrrolidino

a: Z = OCH_2
b: CH_2

i: 1,3-dimethylbarbituric acid, piperidine/AcOH, toluene, rt; ii: dimethyl sulfoxide, Δ.

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