Synthesis and Chemistry of Pyridazines Functionalized in Position 3 and 5 with Heteroatoms

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Dedicated to Professor Gottfried Heinisch on the occasion of his 60th birthday

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Introduction.

For more than three decades we have been interested to a great extent in the synthesis and reactions of six-membered heterocycles with a (usually enolized) 1,3-dicarbonyl moiety, the so-called "malonyl heterocycles". These include for instance 4-hydroxy-2-pyrones, 4-hydroxy-2(1*H*)-pyridones, and their benzo derivatives, the 4-hydoxycoumarin or -2(1*H*)quinolone systems **1**, **2**. Also hydroxy pyrimidones, oxazinones or thiazinones **3** belong to this series, as well as the well known "malonyl α-aminopyridine" of Chichibabin [1], the pyridopyrimidone **4**. Actually, the latter compound exists in water predominantly as a zwitterion [2]. Alkylation studies [3] with **4** led us into the broad field of cross-conjugated mesomeric six-membered heterocycles **5** [4]. Usually, these type of compounds are made from simple malonic acid derivatives, such as malonic acids or their diethyl or dimethyl esters, and 1,3-dinucleophiles (ketones, azomethines, enamines, phenols, anilines, amides, thioamides, amidines, including 2-amino-*N*-heterocycles, *etc.*). However, in some cases reactive malonic acid derivatives [5], such as the bis-2,4,6-trichlorophenyl malonates, "magic malonates", chlorocarbonylketenes, or carbon suboxide (C_3O_2) have to be used.

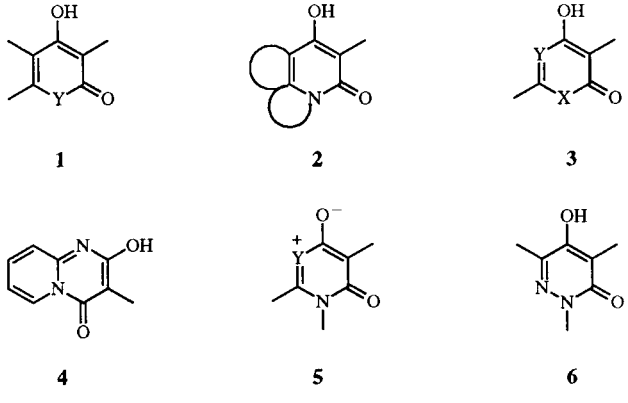


Figure 1. "Malonylheterocycles".

However, there was one "malonyl heterocylic system", the 5-hydroxy-3(2*H*)-pyridzinones **6**, for which we could not find a synthetic route starting from any malonic acid derivative. The system seemed of importance because several derivatives had shown herbicidal activity (in Figure 2 some of the best known are depicted). Fortunately, the manufacturer of PYRIDATE® (CHEMIE LINZ AG) provided kg quantities of the three intermediates **8**, **9**, and **10** for further synthetic studies.

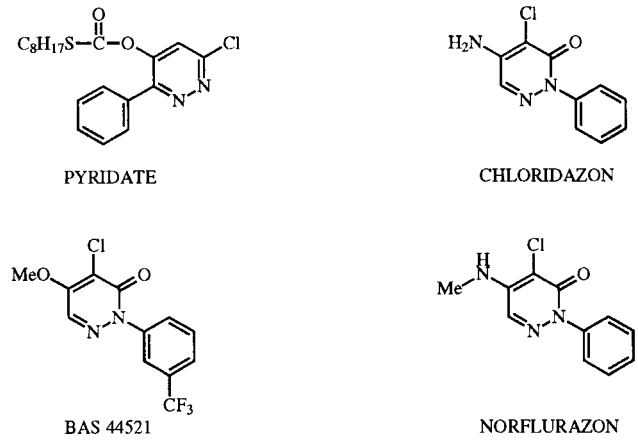


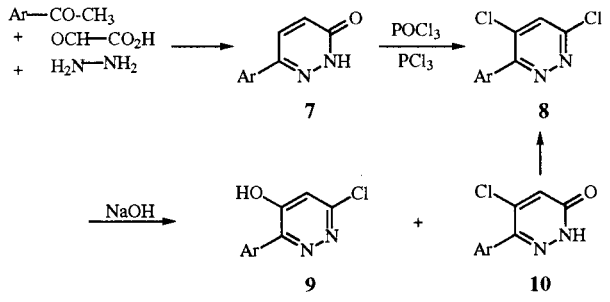
Figure 2. Derivatives of 5-hydroxy-3(2*H*)-pyridazinone used as herbicides.

Synthesis of Starting Materials, Nucleophilic Displacement Reactions.

In Scheme 1 the technical synthesis of the key intermediate **9** for PYRIDATE® is shown. The condensation of acetophenone, glyoxylic acid and hydrazine leads to the 6-aryl-3-pyridazinone **7** which in turn gives with a mixture of phosphorus oxychloride and phosphorus pentachloride the dichloropyridazine **8**. Hydrolysis with sodium hydroxide yields a mixture of **9** and **10** in a 2:1 ratio from which the "undesired" monochloro isomer **10** is returned to the process by rechlorination with phosphorus oxychloride to the dichloropyridazine **8** [6].

Scheme 1

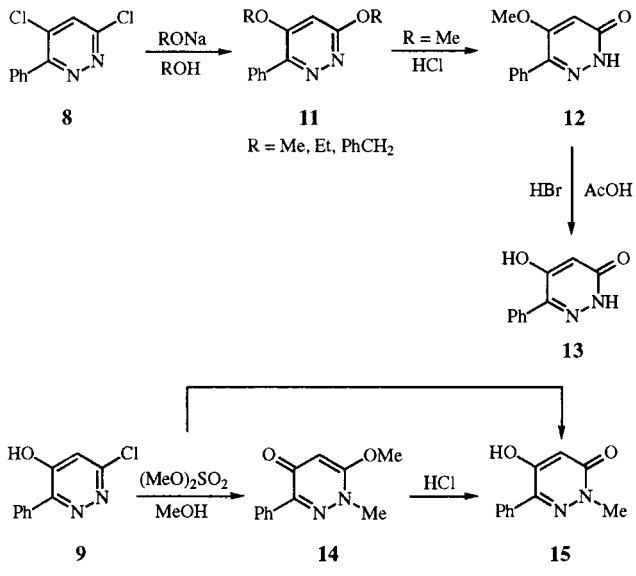
Synthesis of 3,5-Dichloro-6-phenylpyridazine



Conversion of **8**, **9**, or **10** even in molten sodium hydroxide/potassium hydroxide (250-300°) did not yield the desired basic structure **13** (because of anion formation). However, this problem could be circumvented by the action of alkoxides on **8** which leads to dialkoxy products **11**. The reaction with methoxide was scaled up to 100 g quantities with a Soxhlet-extraction technique (neccessary because of the low solubility of **8** in methanol) [7]. For ether cleavage of **11** to yield **13** we developed a simple two step procedure: hydrochloric acid cleaves first the alkoxy group in position 3 and subsequent reaction with hydrobromic acid leads to **13**. Excess of hydrobromic acid and prolonged heating must be avoided since this leads to an increased amount of the reduced pyridazinone **7** as side product [7]. This reduction process is also the reason for choosing the two step procedure: direct action of hydrobromic or even hydroiodic acid on **11** decreases considerably the yield of **13** [7].

Scheme 2

Synthesis of 5-Hydroxy-6-phenyl-3(2*H*)-pyridazinone and its *N*-Methyl Derivative

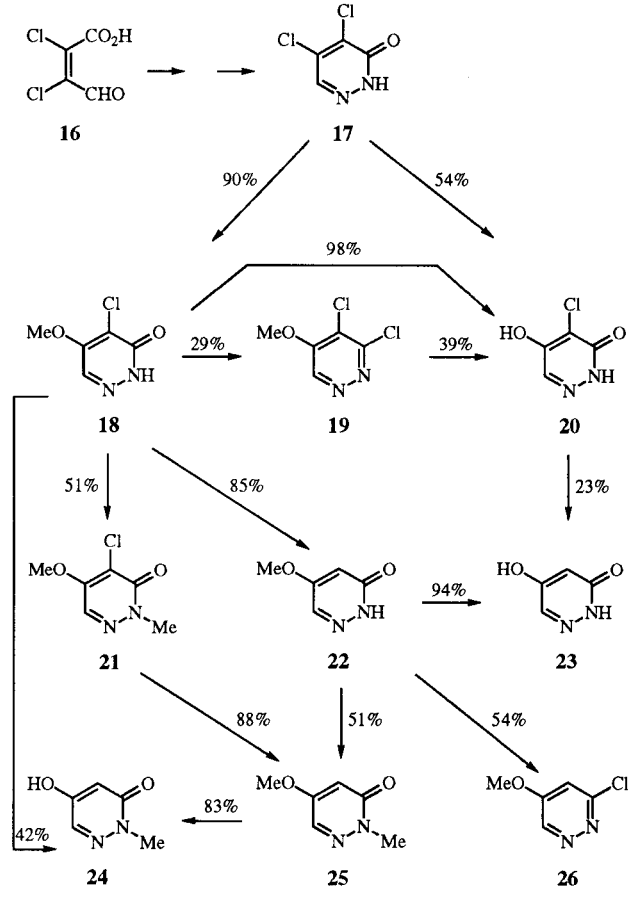


The important *N*-methyl derivative **15** can be obtained by alkylation of the Pyridate® intermediate **9** with dimethyl sulfate in methanol in the presence of sodium hydroxide *via* the 3-methoxy intermediate **14** [8]. Under certain reaction conditions the reaction of **9** with dimethyl sulfate affords directly **15** [8,9].

The pyridazinones **17-26** depicted in Scheme 3 represent the fundamental structures in this series since they contain no aliphatic or aromatic substituent. The dichloropyridazinone **17** is commercially available [10], but the method of its preparation, starting with mucochloric acid (**16**) and semicarbazide published by Castle [11], is very reliable and effective in order to obtain large quantities of **17**. Compound **17** can be converted with phosphorus oxychloride/phosphorus pentachloride to 3,4,5-trichloropyridazine. Since our interest was mainly the synthesis of malonyl heterocycles we were interested to find an easy access to 5-hydroxy-3(2*H*)-pyridazinone **23**. From the many different routes starting with **17** the one depicted in Scheme 3 *via* **18**, and **22** gives the best overall yield [12].

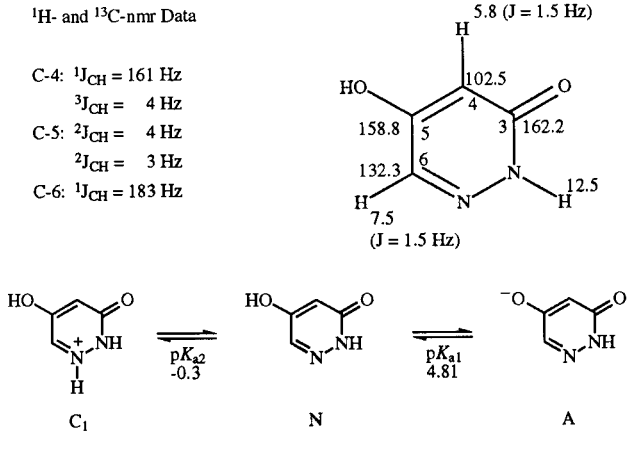
Scheme 3

Synthesis of the Fundamental Structure **23** and Related Substances



It should be mentioned that **23** has previously been synthesized [13], however the last step, the dehydrohalogenation of the free hydroxy derivative **20** afforded only a 8.8% yield of **23** (23% in our hands). It should also be mentioned that some researchers could not repeat our high yield preparation of **18** on a large scale (18 moles) due to precipitation of a pyridazinone salt [14]. They circumvented the problem by protecting the pyridazinone nitrogen as tetrahydropyranyl derivative [14].

Compound **18** is also the starting point for the synthesis of the 2-methyl-5-hydroxy-3(2*H*)-pyridazinone **24**. It can be prepared *via* **21** (or **22**) and **25**, or in a one pot reaction in 42% yield from **18** [12].



Two more tautomeric structures of the cation can be envisaged:

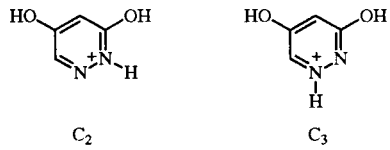
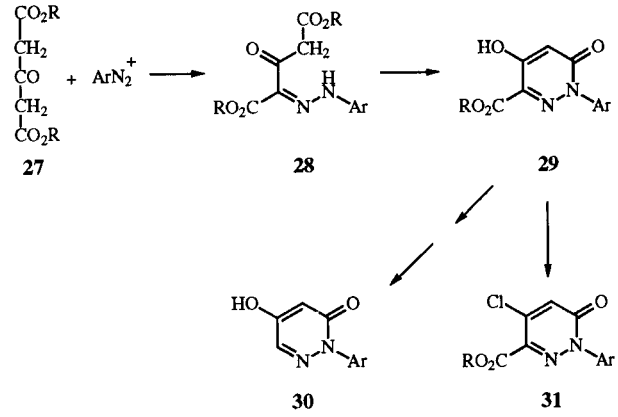


Figure 3. Physical data of the fundamental structure **23**.

X-Ray structure analyses of the basic structures **23**, **24** and **25** have been performed [12]. In Figure 1 the ^{1}H- and ^{13}C-nmr data of **23** are presented. Compound **23** is rather acidic with a p*K*a value of 4.81 (comparable to acetic acid). Protonation occurs with a p*K*a of -0.3, and three tautomeric forms of the cation can be envisaged [12].

Scheme 4

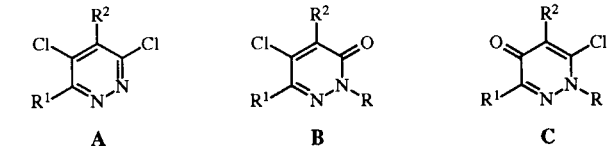
Synthesis of *N*-Aryl-5-hydroxy-3(2*H*)-pyridazinones



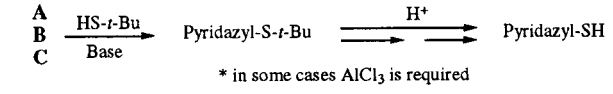
As shown in Figure 2 *N*-arylpyridazinones with amino or alkoxy groups in position 5 are compounds with herbicidal activity. They can of course also be prepared starting with mucochloric acid and arylhydrazines. Another approach starts with aryldiazonium salts and carboxylic acid derivatives with an active methylene group. For our needs we have coupled a variety of diazonium salts with dimethyl acetonedicarboxylate (**27**) producing hydrazones of type **28** which can be cyclized in boiling 1,2-dichlorobenzene to yield the pyridazone esters **29** (R = Me) or in 2 *N* sodium hydroxide solution to give the free acids **29** (R = H) [15]. The acid function can be converted to amides and hydrazides. On the other hand the free acids decarboxylate at elevated temperatures to yield *N*-aryl-5-hydroxy-3-pyridazinones **30** without a substituent in position 6 [15]. The 5-chloropyridazinone **31**, starting material for a number of nucleophilic substitution reactions, is obtained from **29** with phosphorus oxychloride [16].

Scheme 5

Nucleophilic Substitution of 3- and/or 5-Chloro Substituted Pyridazines



Preparation of Mercapto Compounds:



* in some cases $AlCl_3$ is required

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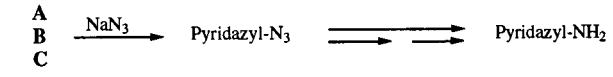
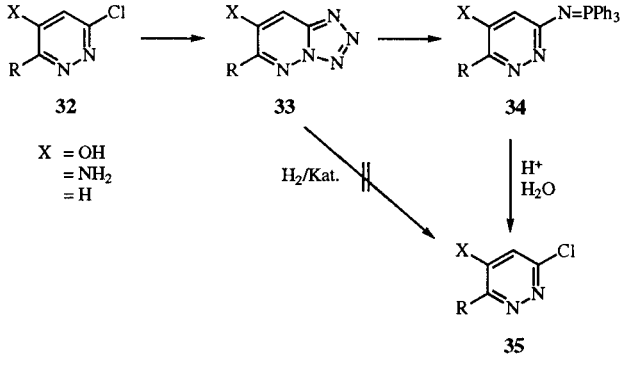
Preparation of Amino Compounds:



Synthesis, 666 (1989)

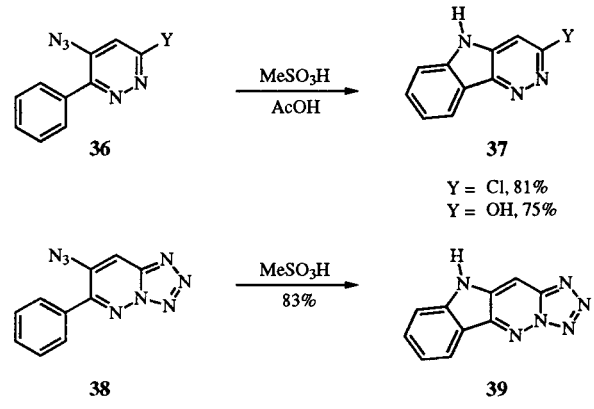
A number of nucleophilic replacement reactions of halopyridazines leading to 3- and/or 5-mercapto [16,17] and amino derivatives [16,18] have been published in part, and are therefore summarized in Scheme 5 only briefly. Primary amines of π-deficient aromatic azines may be obtained by reaction of chloro derivatives with ammonia. However, this procedure requires in most cases the use of an autoclave or sealed tube at elevated temperatures. Alternative routes proceed *via* the corresponding hydrazino or azido derivatives which on hydrogenation afforded the wanted amines. The reaction can preferably be carried out by catalytic hydrogenation, or *via* the Staudinger reaction with phosphines or phosphites (usually triphenylphosphine is used). In this manner phosphazenes are obtained as intermediates which on acid or alkaline hydrolysis yield primary amines and phosphine oxides or phosphates. The Staudinger reduction sequence can also be applied to heterocyclic azides which contain either sensitive halogen, or sulfur substituents (which usually poison the catalyst).

Scheme 6
Staudinger Reduction of Tetrazolopyridazines



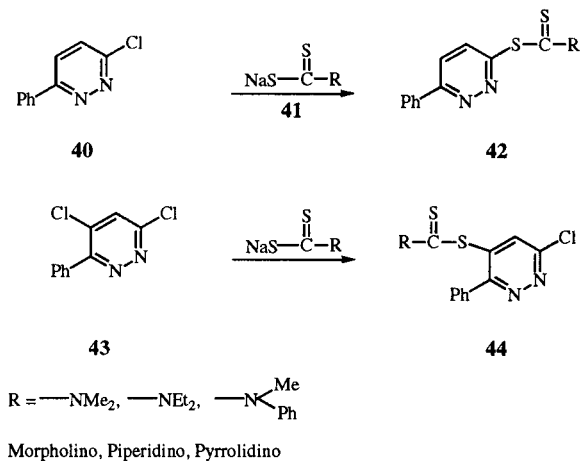
Furthermore, the Staudinger reaction is very important for those azides of azines in which the the azido group is in α-position to one ring nitrogen atom, and if the azido/tetrazole equilibrium [19,20] is totally shifted to the tetrazolo form. It has been shown that phosphines attack the terazolo moiety directly and not *via* a open chain azide tautomer [20]. We have studied these cases in the 2-azidoquinoline and pyridine series [21,22]. In Scheme 6 some results with 3-"azidopyridazines" **33** are shown to demonstrate the usefulness of this approach [18].

Scheme 7
Indoles from *o*-Azidophenylpyridazines



Compounds **36** or **38** with a phenyl substituent in position 6 undergo ring closure under formation of indole ring systems (**37**, **39**) if heated in strong acids, such as sulfuric or hydrochloric acid. Best results are obtained with methanesulfonic acid in acetic acid [23]. Probably nitrenium ions are involved after the release of nitrogen. Most surprisingly, simple thermolysis (successfully used by us [24] with some other classes of *o*-azidophenyl substituted heterocycles) of **36**, **38** did not afford indoles. Also photolysis did not yield indoles with these educts [23].

Scheme 8
Reaction of Chloropyridazines with Dialkylaminodithiocarbamates



In Scheme 5 the introduction of the mercapto group [17] into chloropyridazine and pyridazinones *via* the *tert*-butyl methodology (developed by Becher [25]) has been depicted briefly. The preparation of thioethers is of course

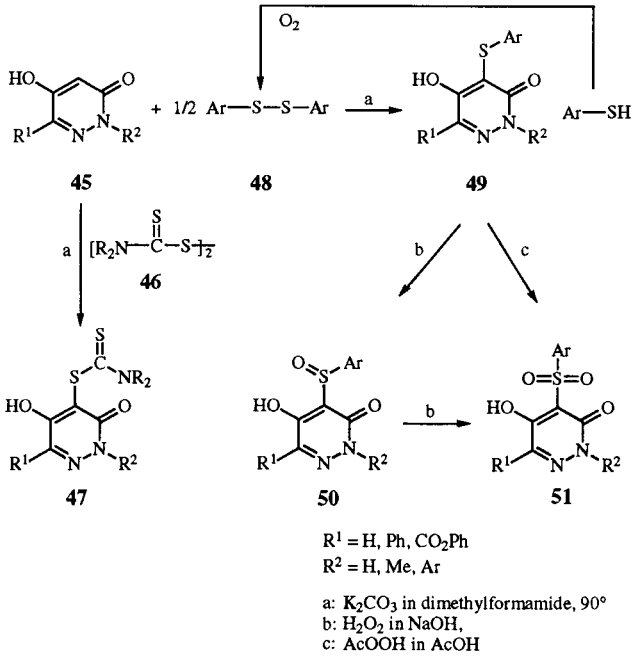
not only limited to other alkyl or aryl mercaptanes [7,18]. Recently we have also used sodium dialkyldithiocarbamates **41** for the displacement of halogen in pyrimidines [26]. An example with 3-chloro and 3,5-dichloropyridazines is shown. Thus the 3-chloro compound **40** leads to the 3-dialkylaminothiocarbonylpyridazine **42**. Interestingly, the 3,5-dichloropyridazine **43** exchanges selectively the chlorine atom in position 5. Even under drastic conditions, the second chlorine atom in **44** can not be exchanged. Obviously, the introduction of the sulfur group reduces the π-deficiency of the pyridazine system drastically [27].

Electrophilic Substitutions and Ring Closure Reactions.

The introduction of sulfur by nucleophilic substitution of reactive halogen atoms at positions 3 and 5 of the pyridazine system is one problem. Another problem is the electrophilic introduction of sulfur containing groups in the electron rich position 4 in 5-hydroxy-3(2*H*)-pyridazinones whose preparations have been described in the preceding chapter. The extremely nucleophilic dialkylaminocarbamate anions **41** used in Scheme 8 (prepared readily by mixing dialkylamines in sodium hydroxide solution with carbon disulfide) can be "umpoled" by oxidation just with hydrogen peroxide in the same medium. The resulting disulfirames **46** react easily with the anions of **45** - produced by the action of potassium carbonate in dimethylformamide - to give the 4-dialkylaminothiocarbonylthiopyridazinones **47** with potential fungicidal activity [28].

Scheme 9

Sulfidation of Hydroxypyridazinones with Disulfides



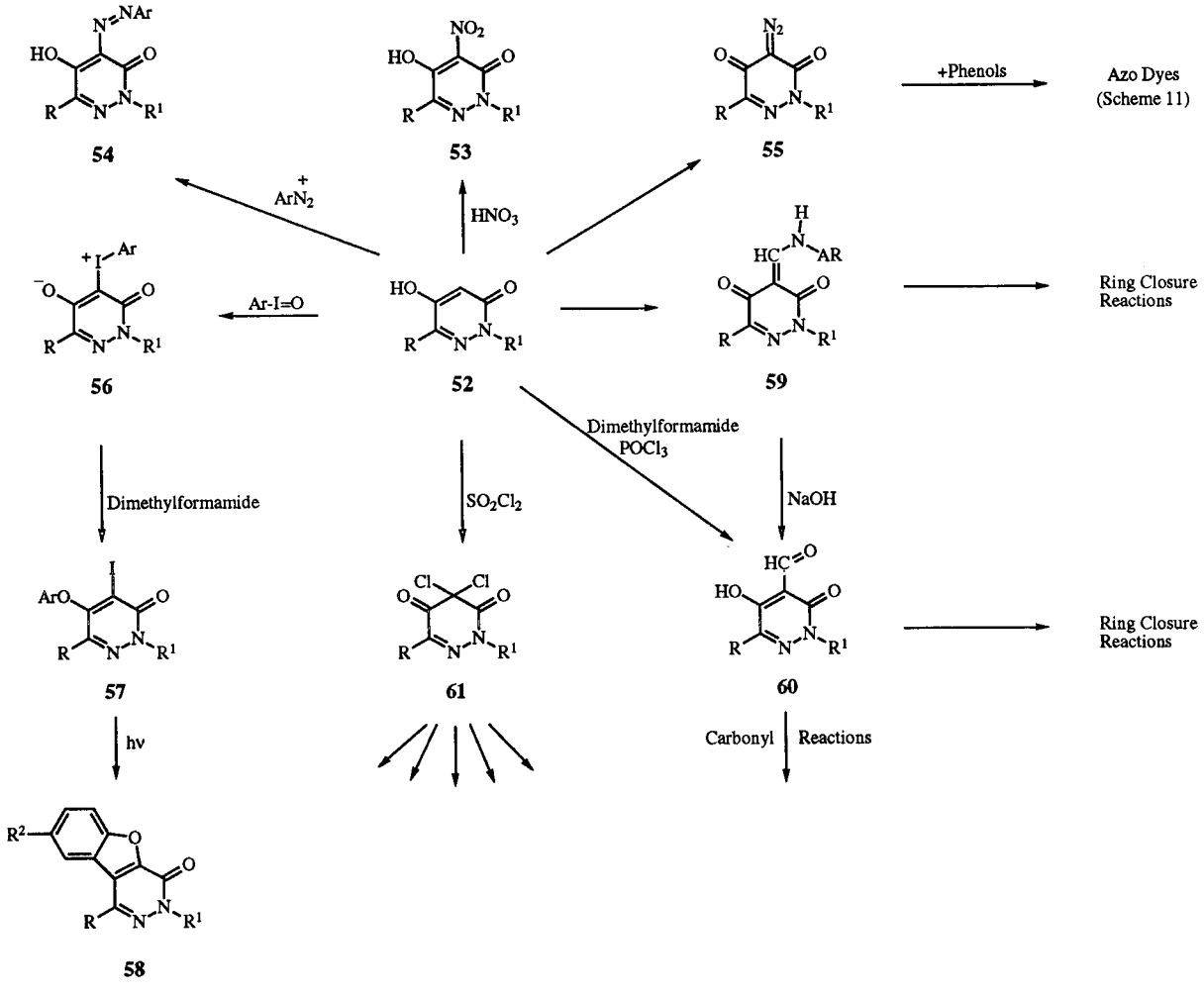
Similarly the reaction of aromatic disulfides **48** with **45** was performed in dimethyl formamide at 90-100° in the presence of potassium carbonate and with rapid stirring [28,29]. When equal amounts of reactants were used a large amount of disulfide was recovered although the yield of products **49** was high. Obviously the expected thiophenol anions were oxidized by atmospheric oxygen to the disulfides again. We adopted a procedure for large scale operation in which only 50% of the disulfide was applied and air bubbled though the reaction mixture [28,29]. The ultimate goal of this research project was however the preparation of aromatic sulfoxides of type **50**. These compounds are heteroanalogs [SO instead of CO] of the so-called tricarbonylmethane systems. Recently some aroyl derivatives of alicyclic and heterocyclic β-dicarbonyl systems have found interest as herbicides [30,31]. Oxidation of sulfides **49** to sulfoxides can be achieved by oxidation with hydrogen peroxide in alkaline medium under well defined conditions. On the other hand, oxidation to sulfones **51** is very easily accomplished in acidic medium [28,29].

Scheme 10 summarizes some other results of electrophilic substitutions of 5-hydroxy-3(2*H*)-pyridazinones **52** (**13**: R = Ph, R^1 = H; **15**: R = Ph, R^1 = Me; **23**: R = R^1 = H; **29**: R = CO_2Me, R^1 = Ar; **30**: R = H, R^1 = Ar). Nitration with nitric acid in acetic acid leads to the nitro derivatives **53**. Coupling of **52** with aryldiazonium salts leads to azodyes. The preparation of the diazo analog **55** could not be achieved using the procedure of Regitz with tosylazide. However, diazo group transfer with 2-azido-1-ethylpyridinium (or quinolinium) tetrafluoroborate was successful (for a further synthesis of **55** and coupling reaction with phenols see Scheme 11). Reaction of **52** with iodosobenzenes (prepared *in situ* from iodobenzene diacetates or dichloroiodobenzenes) yielded the iodonium ylides **56** which readily rearrange to 5-aryloxy-4-iodopyridazinones **57**. Two reactions of **57** should be mentioned: hydrogenolysis with zinc in acetic acid removes the iodine giving aryl ethers of **52** without substituent in position 4; on the other hand photocyclization of **57** in benzene as solvent yields the benzofuro[2,3-*d*]pyridazin-1(2*H*)-one system **58** [8].

Formylation in position 4 of **52** can be achieved by two different routes: The two step synthesis *via* the aminomethylene derivative **59** which can be obtained readily by the "three component reaction" [32] of **52** with trimethyl orthoformate and anilines and subsequent hydrolysis is the most reliable route to afford **60**. The one step synthesis using the Vielsmeier-Haak reaction requires more careful observation of reaction conditions, mainly to avoid chlorination of **52** and **60** [7]. As protected aldehyde, **59** can be used for many synthetic purposes (espe-

Scheme 10

Electrophilic Substitutions of 5-Hydroxy-3-pyridazinones **52** (**13**, **15**, **23**, **29**, **30**)

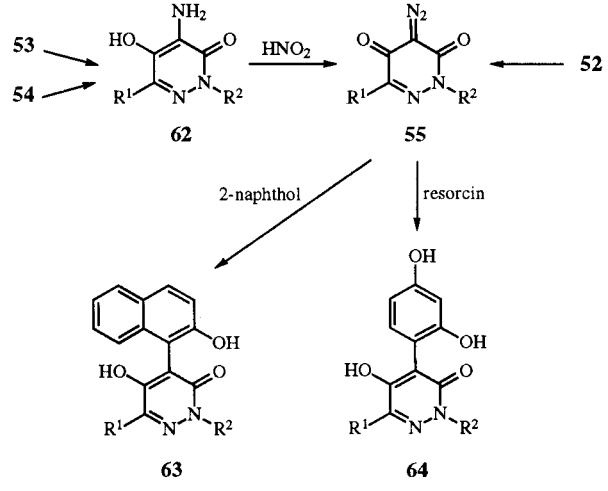


cially condensation reactions, *c.f.* Scheme 12) instead of **60** [7,9]. Reaction of **60** with hydroxylamine gives the oxime which can be dehydrated to the 4-cyano derivative [7].

Iodination and bromination of **52** leads to 4-monoiodo and monobromo derivatives [8,16,33] while chlorination, preferably with sulfuryl chloride, yields the stable dichloro derivatives **61** [8,33,34]. With an excess of bromine a dibromo derivative corresponding to **61** could be obtained and fully characterized, but it proved to be too unstable for further use [8]. The dichloropyridazinediones **61** are extremely useful compounds. Reduction yields the 4-monochloropyridazines, reaction with morpholine affords a 4,4-dimorpholino derivative which can be reduced with sodium dithionite to the 4-monomorpholino compound [8]. The reaction of **61** with pyridine (or isoquinoline) leads to pyridinium ylids (or isoquinolinium ylids). These ylids can also be obtained from the 4-monochloro derivatives, however in lower yields and with longer reaction times [8]. The reaction of **61** with sodium azide in dimethylformamide leads to 4,4-diazidopyridazine-3,5-diones, a very interesting class of compounds [7,8,34,35]. Reduction of this diazide leads to 4-amino-5-hydroxy-3-pyridazinones **62** (see Scheme 11). The thermolysis of the 4,4-diazido substance fits exactly into the general scheme which we have encountered with similar heterocyclic geminal diazides [35]: under the loss of dinitrogen a spirotetrazolyl intermediate is formed which under loss of a second molecule of nitrogen yields the diazido diketone **55** or - if a nucleophile is present - ring opening between C-4 and C-5 occurs [35].

In Scheme 11 again the syntheses of of 4-diazopyridazine-3,5-diones **55** are summarized: (a) diazo group transfer to **52**, (b) diazotation of the amine **62** which in turn can be obtained by reduction of the 4-nitro derivative **53**, or 4-phenylazo dye **54**. As already mentioned also the thermolysis of 4,4-diazidopyridazinediones in an aromatic

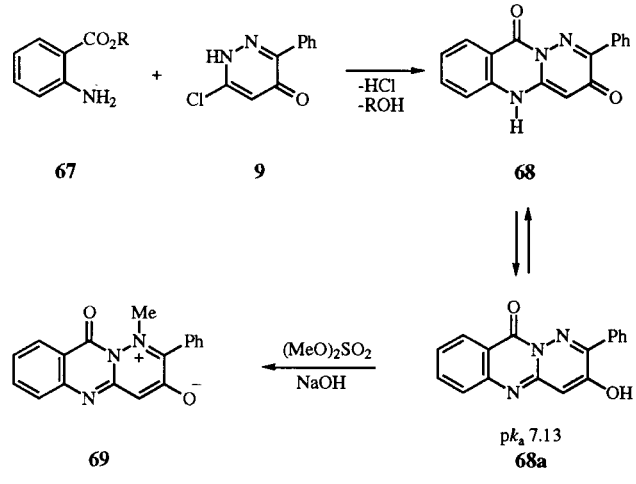
Scheme 11
Coupling of Diazopyridazinedione **55** with Phenols



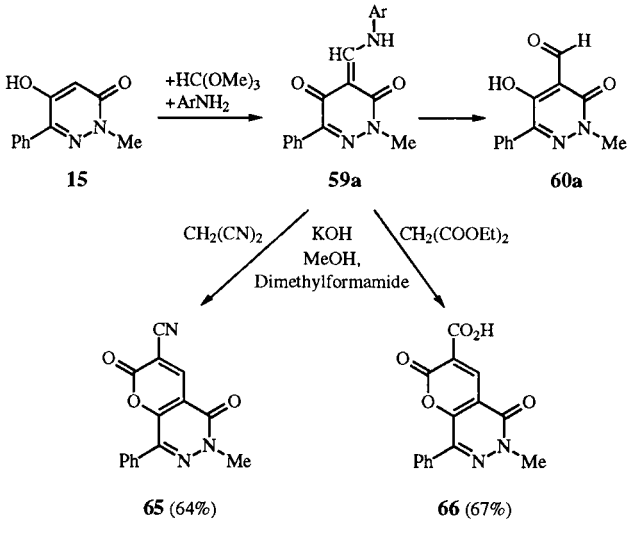
solvent leads to **55**. Coupling with 2-naphthol produces **63**, and with resorcinol **64** is obtained [8]. This phenolic class of azo dyes contains the same basic structure as **54** in Scheme 10. However, these phenolic derivatives can not be obtained by direct coupling of **52** with a diazonium salt. Therfore both methods supplement each other nicely.

3-Anilinomethylene-4-hydroxycoumarins and 2-quinolones react with malononitrile or ethyl cyanoacetate in dimethylformamide at 80-100° with potassium hydroxide as catalyst to pyrano condensed coumarins and 2-quinolones with interesting fluorescence properties [36]. Under the same conditions we obtained with **59a** and malononitrile the expected cyanopyranopyridazinedione **65**, and with ethyl cyanoacetate the acid **66** which was the product of saponification of the ester. The same product was obtained when diethyl malonate was used as the reactant [7].

Scheme 13
Condensation of 3-Chloro-5-pyridazinone with Ethyl Anthranilate

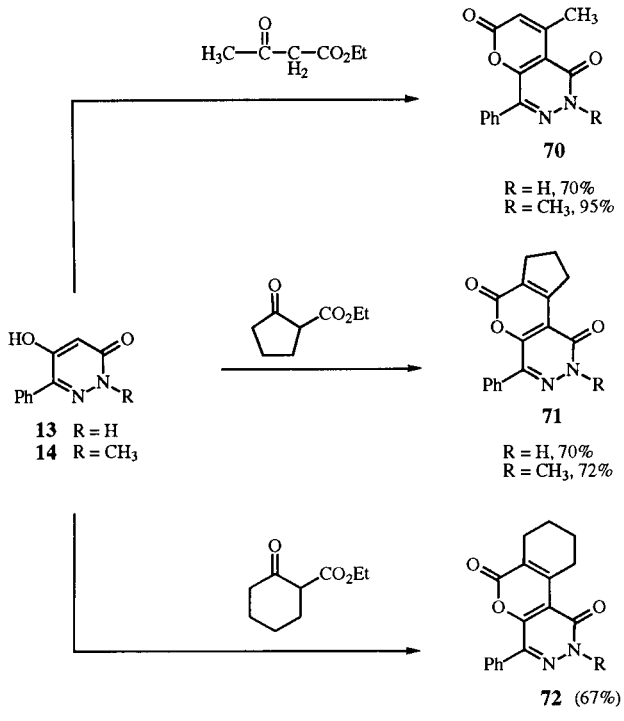


Scheme 12
Ring Closure Reactions of Aminomethylenepyridazinediones



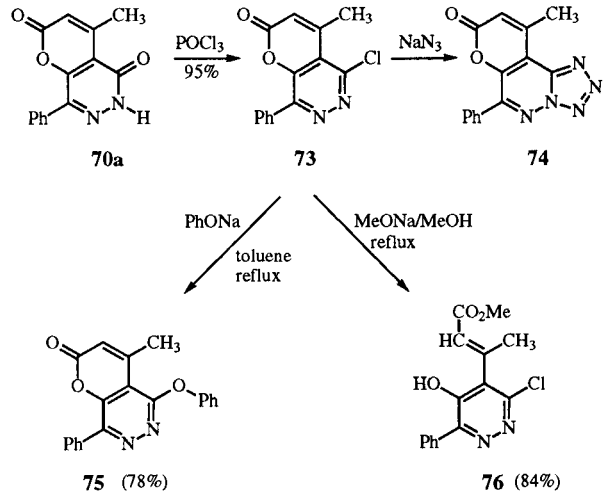
When the active principle of Pyridate®, 3-chloro-5-hydroxy-6-phenylpyridazine **9** (represented in Scheme 13 as a tautomeric pyridazinone) is condensed with ethyl anthranilate the pyridazoquinazolinone system **68** is formed [37]. The compound showed herbicidal activity comparable to Pyridate®, most probably by a different biological mechanism [38]. However, application of the compound was difficult due to its low solubility in most solvents. The compound shows a pK_a of 7.13 which led us to consider also the enolic structure **68a**. In fact a number of esters (including carbonates and urethanes) derived from this structure have been prepared [37]. On the other hand, we had difficulties in establishing the structure of methylation products. This problem has very recently been solved by the Hajós group [39]. According to their results a mixture of N-5 and O-3 methylated compounds are formed when the reaction is carried out in dimethylformamide/potassium carbonate, whereas in aqueous medium the zwitterion **69** is obtained in high yield [39].

Scheme 14
Condensation for 5-Hydroxy-3-pyridazinones with β-Ketoesters



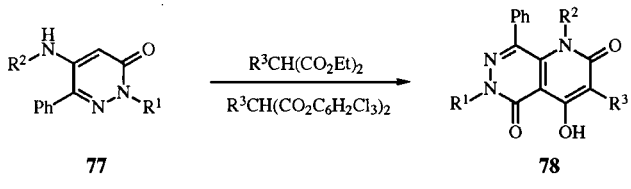
The stepwise annelation of a pyranone ring to the pyridazinone system is described in Scheme 12. Synthesis of higher substituted pyranone derivatives can be accomplished by condensation of 5-hydroxy-3-pyridazinones with β-ketoesters. Thus the Pechmann condensation of **13** and **15** with ethyl acetoacetate, cyclopentanone-2-carboxylates and cyclohexanone-2-carboxylates in boiling 1,2-dichlorobenzene in the presence of ammonium acetate affords the pyranopyridazinediones **70-72** in good yields [7], as shown in Scheme 14. The Pechmann condensation of phenols with β-ketoesters to yield coumarins is usually catalized with Lewis acids [40]. Some time ago we have modified the reaction conditions by converting the β-ketoester first to a β-enaminoester which can be condensed with a phenolic compound at about 150-180° [41]. It was then discovered that the β-enamino esters are not neccessarily required and that the addition of an excess of ammonium acetate to β-keto esters is in most cases sufficient to effect condensation [40,42]. This modification of the Pechmann reaction is especially useful in the series of phenolic heterocycles [42].

Scheme 15
Further Reactions of Pyrono Fused Pyridazinones



The reactions of **70a** may serve as an example for further transformations of pyranopyridazinediones which still have a proton at the nitrogen atom. As shown in Scheme 15 the action of phosphorus oxychloride leads to **73**. The chlorine can be exchanged with sodium azide to afford the tetrazoloazine **74** which can be reduced by the Staudinger method to the corresponding amino derivative [7]. Nucleophilic substitution with sodium phenolate in refluxing toluene affords the phenyl ether **75**. Interestingly, a similar reaction with sodium methoxide in refluxing methanol did not yield the corresponding methyl ether, but the methyl acrylate **76** with no exchange of the chlorine atom [7].

Scheme 16
Condensation of 5-Amino-3-pyridazinones with Malonates



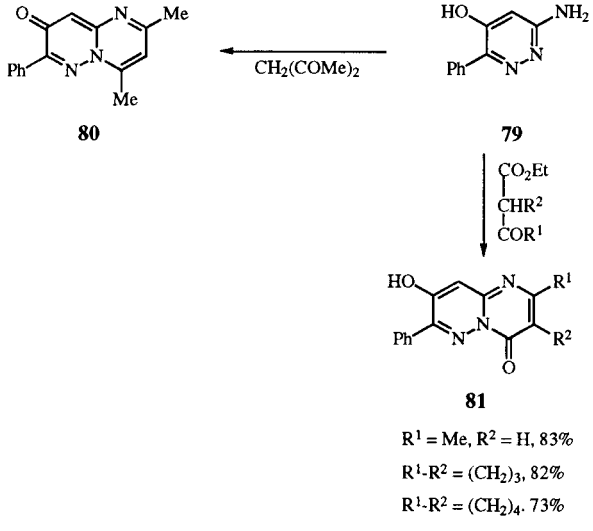
R^1	R^2	R^3	Yield
H	Phenyl	Phenyl	30%
H	Benzyl	Phenyl	51%
H	H	Phenyl	76%
H	H	Butyl	73%
H	Phenyl	Butyl	55%
H	Phenyl	Benzyl	61% [a]
Methyl	H	Phenyl	82%
Methyl	Phenyl	Phenyl	40%
Methyl	Benzyl	Phenyl	71%
Methyl	H	Butyl	62%
Methyl	H	H	38% [a]
Methyl	Phenyl	Carbethoxy	64%
Methyl	H	Carbethoxy	76%

[a] Bis-2,4,6-trichlorophenyl malonate

Scheme 16 shows the condensation of 5-amino-3-pyridazinones **77** with malonates. The starting primary amines **77** (R^2 = H) have been prepared from the 5-chloro-3-pyridazinones by azide exchange and subsequent hydrogenation with a palladium catalyst, or Staudinger reduction *via* phosphazenes [18]. The benzyl and phenylamines are obtained simply by heating of the chloropyridazinones with benzylamine or aniline [37]. Generally, the use of diethyl malonates affords good yields of **78**. Only for the praparation of **78** with R^1 = Me, R^2 = R^3 = H, the unsubstituted bis-2,4,6-trichlorophenyl malonate [5a] had to be used [37]. On the other hand also triethyl methanetricarboxylate reacted like a substituted diethyl malonate yielding **78** with an ethoxycarbonyl substituent at position 3 [37]. We have reported previously [16] the malonate condensation of a primary 5-amino-2-phenyl-3-pyridazinone and with a carbethoxy group (instead of the phenyl group) at position 6. Also in that case the use of bis-2,4,6-trichlorophenyl malonate was required [16].

Scheme 17

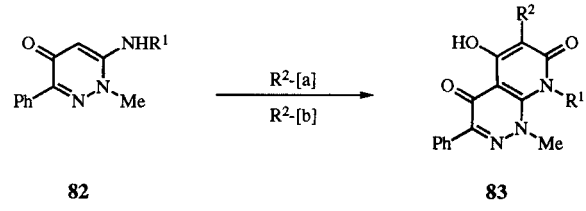
Condensation of 3-Amino-5-hydroxypyridazines with Pentane-2,4-dione and with β-Ketoesters



3-Amino-5-hydroxypyridazine **79** is readily condensed with some 1,3-dicarbonyl reagents (Scheme 17). Thus, the reaction with acetylacetone at 135° affords in 80% yield the pyrimidopyridazinone **80**. Condensation with β-keto esters leads to **81**. The tricyclic derivative **81** with R^1-R^2 = -$(CH_2)_4$- (obtained with ethyl cyclohexanone-2-carboxylate) represents the tetrahydro derivative of the biological active **68** (see Scheme 13). Unfortunately, this compound shows no herbicidal activity; it also could not dehydrogenated to **68** [34].

Scheme 18

Condensation of 3-Amino-2-methyl-5-pyridazinones with Malonates



R^1 = H, R^2 = Ph,	88%	[b]
R^1 = R^2 = Ph,	60%	[a]
R^1 = H, R^2 = *n*-Bu,	63%	[b]
R^1 = R^2 = H,	71%	[b]

[a] Bis-2,4,6-trichlorophenyl malonate; [b] Diethyl malonate.

Scheme 18 depicts the condensation of malonates with 3-amino-5-pyridazinones **82** in which the N-2 atom is blocked with a methyl group. In this case only pyrido[3,2-*c*]pyridazinediones **83** can be obtained (*e.g.* Scheme 21). Compound **83** with R^1 = R^2 = H could not be prepared with diethyl phenylmalonate, and required the use of the corresponding bis-2,4,6-trichlorophenyl malonate [37]. The reason for this may be the reduced nucleophilicity of the phenylamino substituent, steric hindrance, and/or the possibility of a side reaction to a quinolone system (similar to a reaction shown in Scheme 23).

Scheme 19

Condensation of 5-Hydroxy-3-pyridazinones with Malonates

13 R^1 = H [a]

15 R^1 = Me [a] or [b]

84

		Yield	
R^1	R^2	[a]	[b]
H	Ph	89%	–
H	Benzyl	84%	–
H	*n*-Butyl	87%	–
H	*n*-Propyl	83%	–
H	Et	80%	–
H	Me	97%	–
Me	Ph	70%	55%
Me	Benzyl	67%	44%
Me	*n*-Butyl	81%	46%
Me	*n*-Propyl	73%	37%
Me	Et	76%	41%
Me	Me	93%	24%
Me	H	–	44%

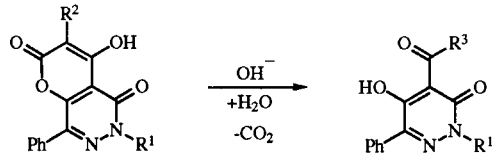
[a] Bis-2,4,6-trichlorophenyl malonate; [b] Diethyl malonate.

4-Hydroxy-2-pyrones fused to hetrocyclic systems represent a very important class of compounds used mainly as intermediates for the preparation of heterocyclic tricarbonylmethane derivatives of biological interest [43,44]. In the pyridazine series compounds **13**, **15**, and **29** have been used for condensation reactions with malonates. The table in Scheme 19 reveals that **13** can only be condensed with the "magic malonates" (bis-2,4,6-trichlorophenyl malonates) [5a], while the *N*-methyl derivatives **15** react also with simple diethyl malonates to yield pyrano[2,3-*d*]-pyridazine-2,5-diones **84** [37]. It can also be seen from the table that the yields with diethyl malonates are lower than those obtained with the bis-trichlorophenylmalonates. But surprisingly, **84** unsubstituted in position 2 (R^2 = H) can only be prepared with diethyl malonate (44% yield). Obviously the unsubstituted bis-2,4,6-trichlorophenyl malonate is too reactive and condenses further with the pyranopyridazinediones to yield polypyranone substances. The pyrone **84** (R^2 = H) is for instance easily nitrated in position 3 with nitric acid in acetic acid [37]. The preparation of more pyranopyridazinediones starting with **29** and using bis-2,4,6-trichlorophenyl malonates as reagents has been described [15].

Action of 1-2 *N* sodium hydroxide solution opens the lactone ring of **84** and the resulting β-keto acids decarboxylate after acidification to **85** [45]. Compounds **85** belong to the heterocyclic series of tricarbonylmethane derivatives with an aliphatic acyl group [30,44,46]. Some of them occur in nature, some synthetic substances have shown interesting biological activity. Recently some synthetic aroyl analogs have found interest because of their biological activity [30,31]. Unfortunately, the important 4-acetyl derivatives of **85** (R^2 = H) could not be obtained by this methodology nor by Fries rearrangement. Strangely enough, the *N*-methyl derivative was obtained by chance when the dimethylurethane derivative of **84** (R^1 = Me, R^2 = H) was heated in dimethylformamide in the presence of some water and pyridine [37]. Compounds **85** have been also converted to oximethers (allyl, benzyl, and methyl) and were tested for their herbicidal activity since they show structural analogy to Alloxidim® and Sethoxidim® [30]. Their thermal Beckmann rearrangement [31,46] resulted as expected in the formation of the corresponding pyridazino[4,5-*d*]oxazole-4(5*H*)-ones [45].

Scheme 20

Degradation of Hydroxypyranopyridazinediones



84

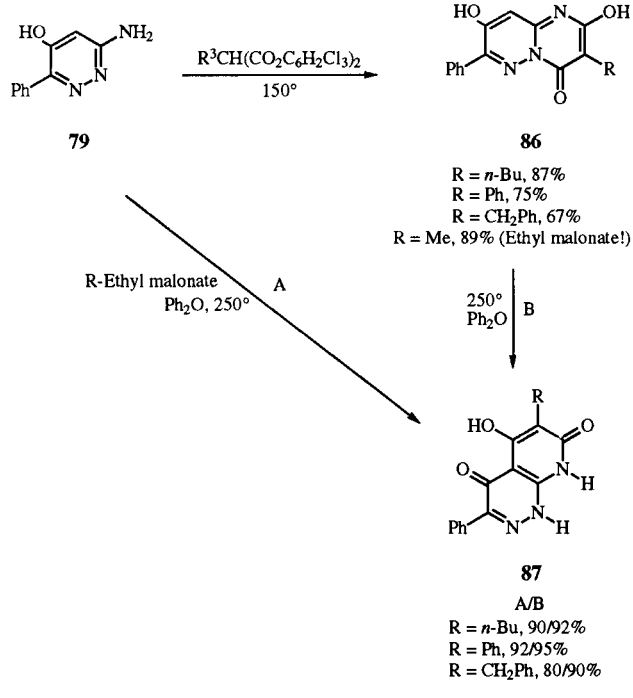
R^1 = H, R^2 = Ph
R^1 = Me, R^2 = Ph
R^1 = Me, R^2 = Me
R^1 = H/Me, R^2 = H

85

R^1 = H, R^2 = CH_2Ph, 69%
R^1 = Me, R^2 = CH_2Ph, 76%
R^1 = Me, R^2 = C_2H_5, 71%
R^1 = H/Me, R^2 = H, 0%

Scheme 21

Condensation of 3-Amino-5-hydroxypyridazine with Malonates and Subsequent Rearrangement



79

86

R = *n*-Bu, 87%
R = Ph, 75%
R = CH_2Ph, 67%
R = Me, 89% (Ethyl malonate!)

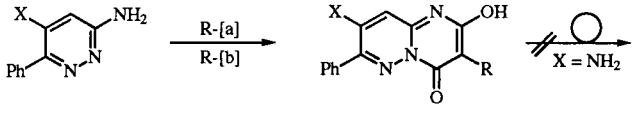
87

A/B
R = *n*-Bu, 90/92%
R = Ph, 92/95%
R = CH_2Ph, 80/90%

The condensation of 3-amino-4-hydroxypyridazine **79** with a 1,3-diketone and β-ketoesters has already been described (*cf.* Scheme 17); the pyrimido[3,2-*b*]pyridazine system (**80**, **81**) is formed with these reagents. A similar result is obtained when "magic malonates" are condensed in boiling bromobenzene (150-155°) with **79**: the 2,8-dihydroxypyrimido[3,2-*b*]pyridazine-4-ones **86** are formed [34]. When heating these compounds for 5 minutes in boiling diphenyl ether (250°, Method B) rearrangement *via* α-oxoketenes (a well known mechanism [4,47]) takes place, and the thermodynamically more stable 5-hydroxypyrido[2,3-*c*]pyridazine-4,7-diones **87** are formed in over 90% yield [34]. These pyridopyridazines **87** are also obtained when **79** is condensed with the corresponding diethyl malonates for one hour in refluxing diphenyl ether (Method A). However, there is one exception which we do not understand: with diethyl methylmalonate under the conditions of method A and method B only **86** (R = Me) is formed. Reaction of **79** with bis-2,4,6-trichlorophenyl α-methylmalonate at 250° affords also the same product!

Scheme 22

Condensation of 3-Amino-5-chloropyridazine and 3,5-Diaminopyridazine with Malonates



88

X = Cl, NH_2

89

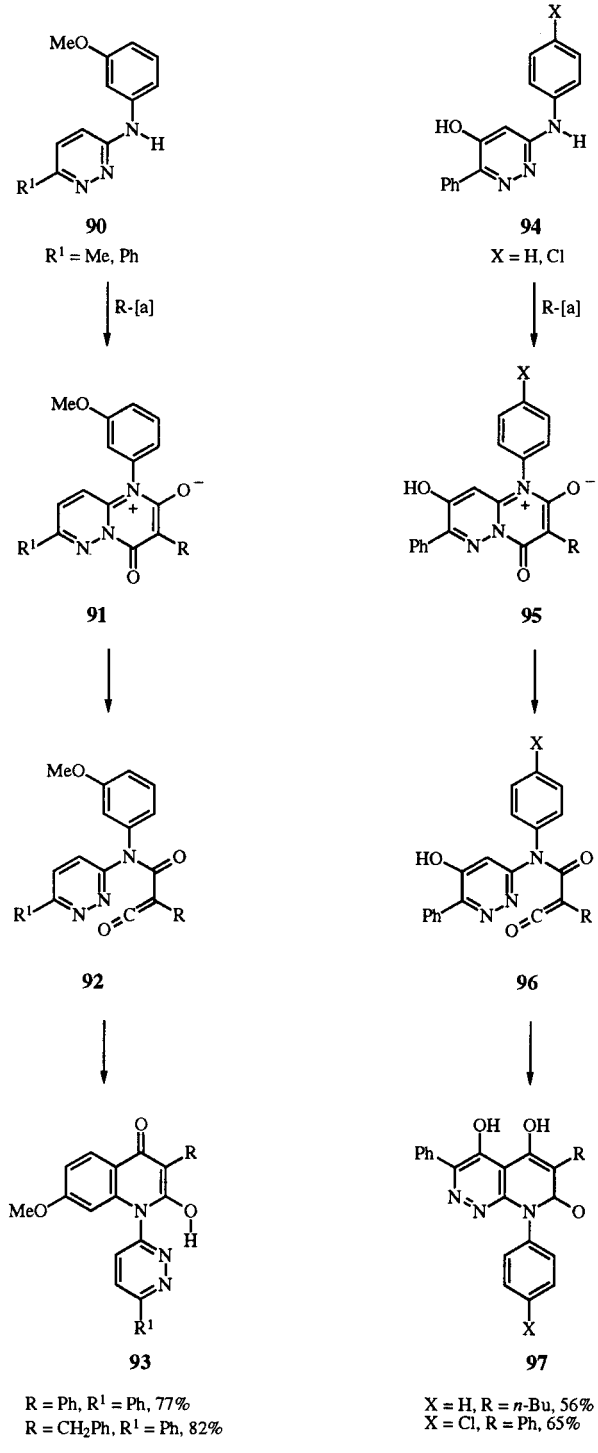
X = Cl, R = Me, 83% [a]
R = Ph, 74% [a]
X = NH_2, R = Ph, 71% [b]
R = CH_2Ph, 64% [b]
R = *n*-Bu, 61% [b]
R = H, 68% [b]

[a] Bis-2,4,6-trichlorophenyl malonate; [b] Diethyl malonate.

In Scheme 22 the condensation of 3-amino-5-chloropyridazine and 3,5-diaminopyridazine is described. The reaction of **88** (X = Cl) requires trichlorophenyl malonates as reagents in boiling bromobenzene (150-155°) to yield **89** (X = Cl), at higher reaction temperatures decomposition takes place. The diamino derivative **88** (X = NH_2) reacts at the same temperature in the same solvent to afford **89** (X = NH_2), however, only diethyl malonates are required, and also the unsubstituted diethyl malonate affords the product **89** (X = NH_2; R = H) in 68% yield. But much to our surprise no rarrangement takes place even at longer reaction times in boiling diphenyl ether or when bis-2,4,6-trichlorophenyl malonates are used for the synthesis at 260° [34]. The enamine C-atom in position 9 should be electron rich as the enolic C-atom in position 9 of the analogs **86** (Scheme 21).

Scheme 23

Rearrangement of Cross-conjugated Mesomeric Pyridopyridazines



90

R^1 = Me, Ph

94

X = H, Cl

91

95

92

96

93

R = Ph, R^1 = Ph, 77%
R = CH_2Ph, R^1 = Ph, 82%

97

X = H, R = *n*-Bu, 56%
X = Cl, R = Ph, 65%

[a] Bis-2,4,6-trichlorophenyl malonate.

In order to perform a more detailed study of rearrangement reactions of mesomeric heterocyclic betaines [4] in which acylketenes (α-oxoketenes) [4,47] are involved we

have selected two new series of mesomeric pyrimido[3,2-*b*]-pyridazine betaines **91**, **95** [48]. The compounds were prepared in the usual way with bis-2,4,6-trichlorophenyl malonates [5a] from two types of 3-anilinopyridazines **90** and **94**. In educt **90** the aniline substituent is made more electron rich with a *m*-methoxy group and the pyridazine system is kept π-deficient. In educt **94** the aniline has no substituent or a *p*-chlorine atom but the pyridazine part is made more electron rich with an hydroxyl group in position 5. When heated above 250° both betaines **91** and **95** are expected to produce similar ketene intermediates **92** and **96**. The ketene intermediate **92** reacts as expected from an earlier and very similar experiment (with a mesoionic pyridopyrimidine derived in a similar fashion from 2-anilino-pyridine [49]): the α-oxoketene attacks the aniline ring in the *ortho*-position (which is *para* to the methoxy group) leading to the hydroxyquinolone system **93**. On the other hand, the ketene **96** finds a better electron rich *ortho*-position: the enolic C-atom in position 4 of the pyridazine system (*cf.* Scheme 21) which leads to the pyridopyridazinone **97** [48].

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