INTRODUCTION

PHTHALAZINONES

Phthalazinone moiety exhibit two lactam-lactim tautomeric forms (1) and (2).

(1) (2)

It's of interest to study synthesis, chemical reactivity and biological action of some phthalazinone derivatives.

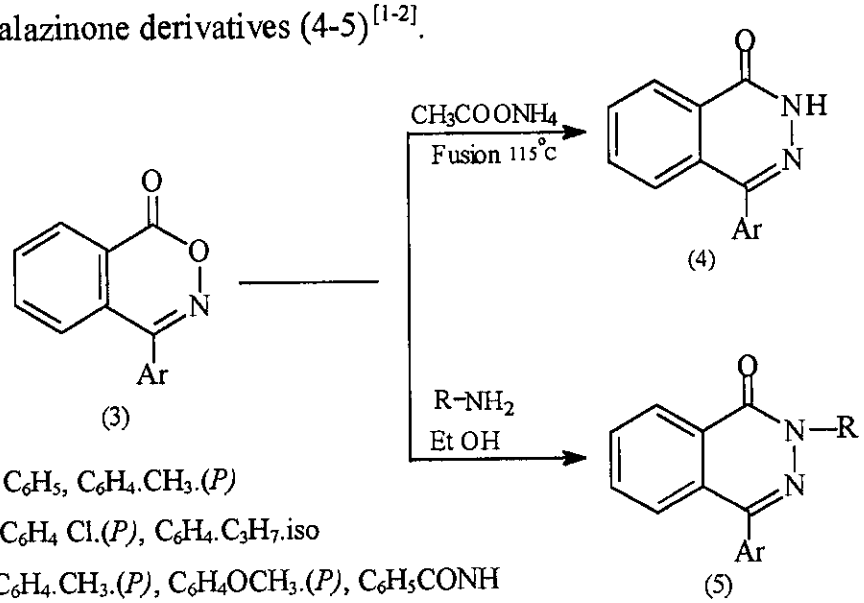
Synthesis of Phthalazinone:

Hydrazine derivatives play a great role in the synthesis of phthalazinones. In most of the reported cases, the reaction involved the direct reaction between hydrazine derivatives with aromatic carbonyl compounds, acid anhydrides, acid imides and oxazines. The reaction usually proceeds via either direct condensation between hydrazines and the substrate or replacement of an oxygen atom by hydrazine's nitrogen atom or both.

Phthalzinone derivatives can be synthesized from:

(1) 3,2-Benzoxazine-4-one

3,2-benzoxazin-4 one (3) reacted with ammonium acetate at 115° C and with *p*-toluidine, *p*-anisidine and benzoylhydrazine in boiling ethanol to give phthalazinone derivatives (4-5)[1-2].

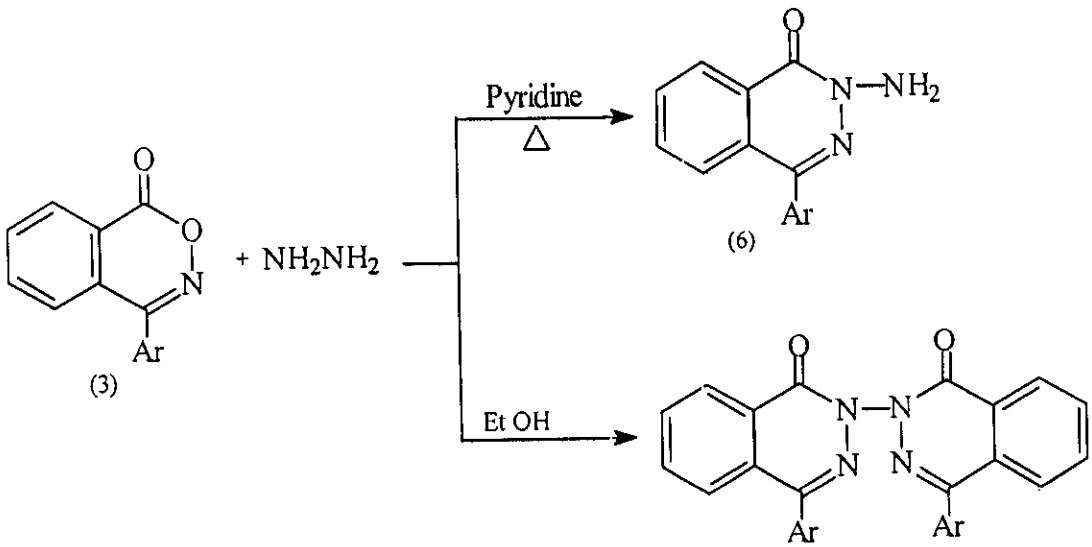


(3) (4) (5)

Ar = C_6H_5, $C_6H_4.CH_3$.(*P*)
C_6H_4 Cl.(*P*), $C_6H_4.C_3H_7$.iso

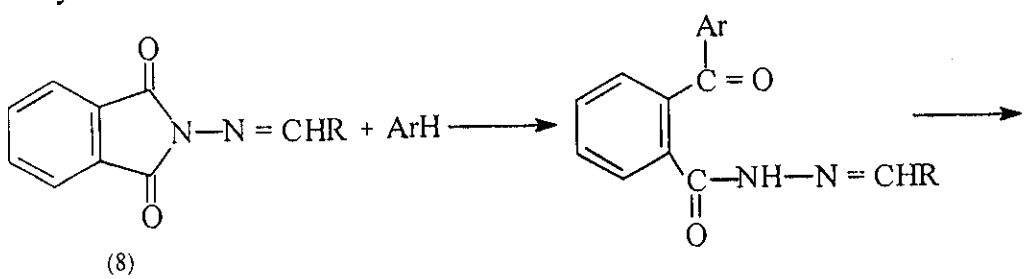
R = $C_6H_4.CH_3$.(*P*), $C_6H_4OCH_3$.(*P*), C_6H_5CONH

Reaction of 3,2-benzoxazin-4-one (3) with hydrazine hydrate in boiling pyridine afforded the expected phthalazinone derivatives(6)[3]. However, carrying out the same reaction in ethanol gave bisphthalazinone (7)[1].

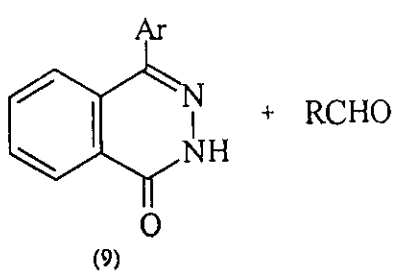


(2) Phthalimide derivatives

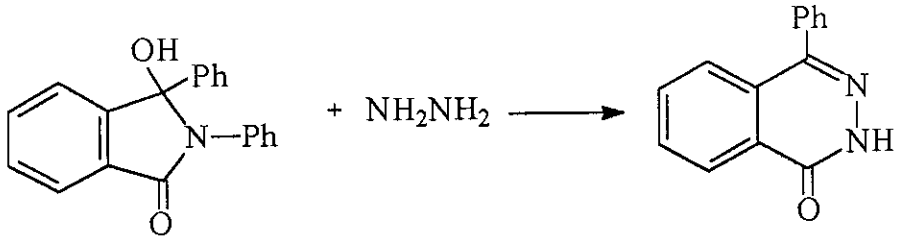
Reaction of N-aminophthalimides such as N-(methyleneamino) phthalimide (8) with aromatic hydrocarbon under Fridel-Crafts conditions followed by hydrolysis gave aryl phthalazinone derivatives (9)[4-5]. The reaction involved ring cleavage followed by cyclization and elimination of an aldehyde moiety.



R = C_6H_5, $C_6H_3(OMe)_2$-3,4
4-Cl.C_6H_4, 4-MeO.C_6H_4
Ar = C_6H_5, C_6H_4. Me *(p)*
C_6H_4, .Br*(P)*. C_6H_4. MeO *(P)*

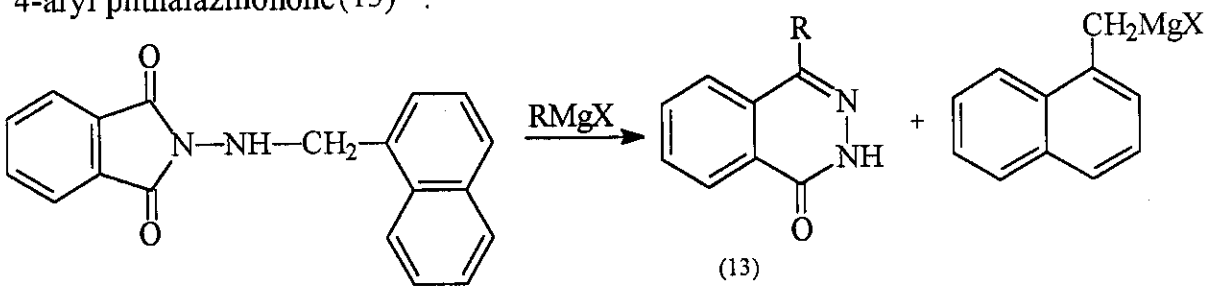


Phenyl phthalazinone (11) was also synthesized by treatment of 2,3-diaryl-3-hydroxy phthalimidine (10) with hydrazine hydrate[6].



(10) (11)

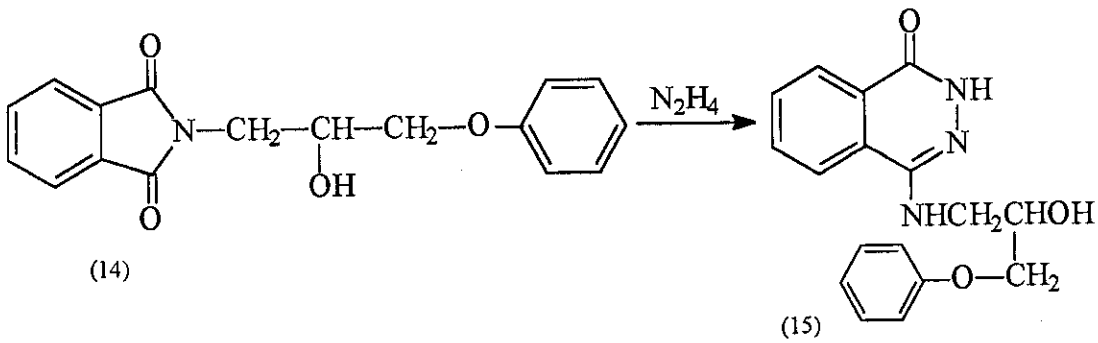
Condensation of N-[(naphthylmethylene)amino] phthalimides (12) with Grignard reagent took place either by normal addition to one of the carbonyl groups to give aryl-N-[(naphthyl methylene) amino] phthalimide or to give 4-aryl phthalazinonone(13)[7].



(12) (13)

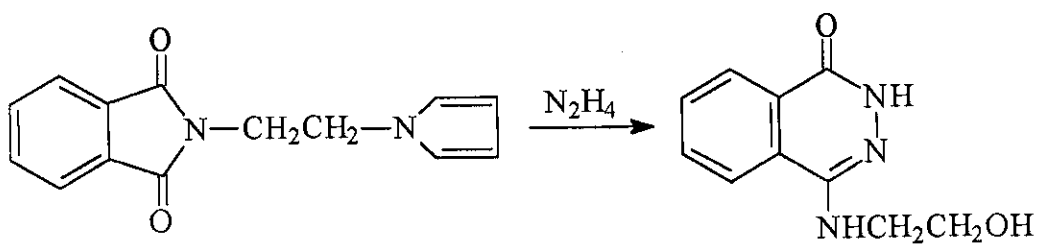
R = C_2H_5, 2or 4-Me. C_6H_4

N-substituted amino phthalazinones was prepared by reaction of hydrazine with N-phthalimide. Thus, treatment of 1-(N-phthalimide)-2-hydroxy-3-phenoxypropane (14) with hydrazine hydrate in methanol led to the formation of 4-(γ-phenoxy-β-hydroxypropylamino)-1 (2H)-phthalazinone (15) [8].



(14) (15)

Also, treatment of 1-(2-phthalimidoethyl) pyrrole (16) with hydrazine hydrate afforded 4-(2-hydroxyethylamino)-1(2H)-phthalazinone (17)[9].

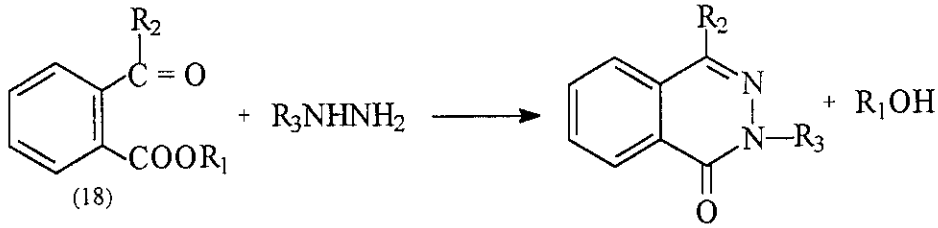


(16) (17)

(3) o-Acylbenzoic acids

o-Acylbenzoic acid derivatives (18) reacted with hydrazines namely hydrazine hydrate, phenyl hydrazine and hydrazine acetate salts, and methallyl hydrazine in boiling butanol or ethanol to form 2-substituted phthalazinones (19)[10-14].

Also it has been reported that acid (18) reacted with semicarbazide, thiosemicarbazide and acylhydrazine in pyridine forming phthalazinone derivatives [15].



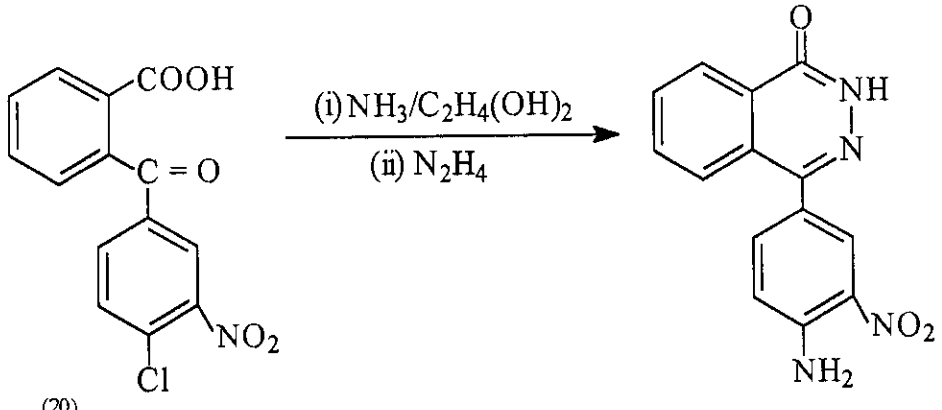
(18) (19)

R_1 = H, alkyl

R_3 = H, C_6H_5, $CH_2—C(CH_3)=CH_2$, $CONH_2$, $CSNH_2$, $COOC_2H_5$

R_2 = CH_3, 4-Cl. 3-Me·C_6H_3, $C_6H_4 \cdot C_6H_5$

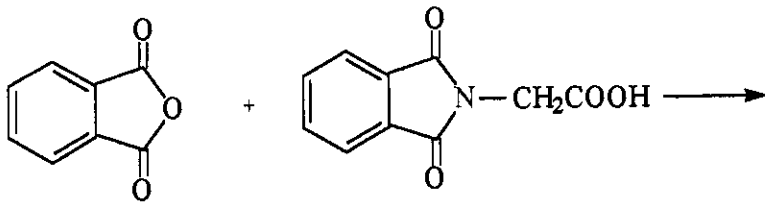
On the other hand reaction of 3-nitro-4-chlorobenzophenon-2-carboxylic acid (20) with NH_3(g) at 120 °C in ethylene glycol followed by treating the reactions mixture with hydrazine hydrate at 79-80 °C afforded 4-(3-nitro-4-aminophenyl)-1(2H) phthalazinone (21)[16].

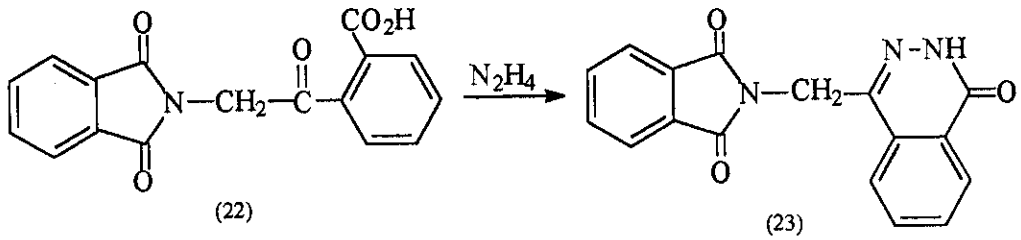


(20) (21)

(4) Phthalic acid derivatives

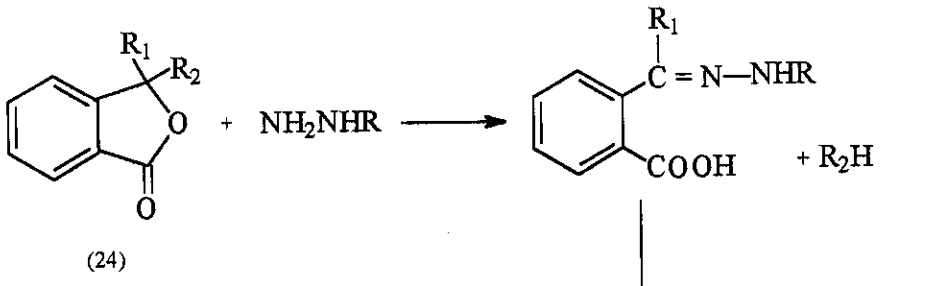
Condensation of phthalic anhydride with phthalyl glycine gave phthalimido-acetophenone derivatives (22) which underwent cyclo condensation with hydrazine to give (phthalimidomethyl) phthalazinone (23)[17].





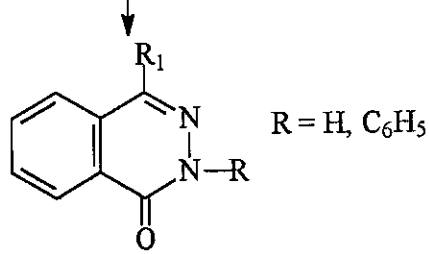
(22) (23)

On treatment of phthalides (24) with hydrazine derivatives, the corresponding phthalazinone derivatives (25) were produced[18-24].



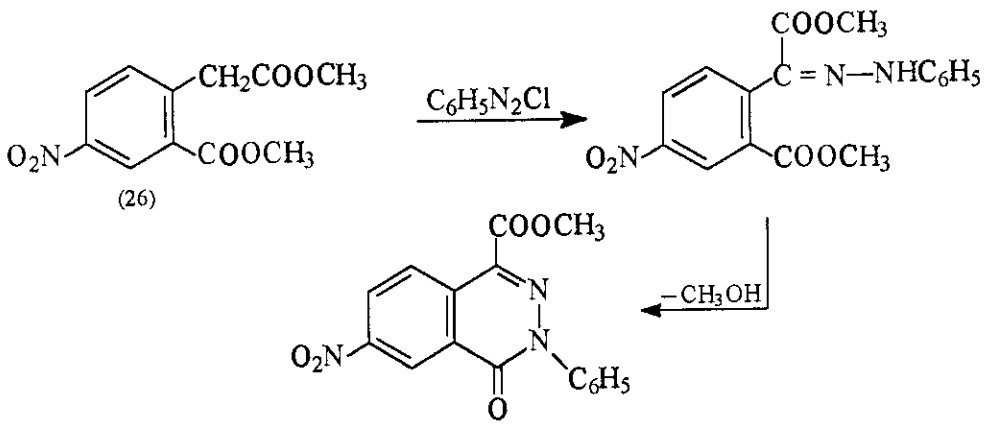
(24)

R_1 = H, alkyl, aryl, pyridyl
R_2 = halogen, NH_2, Ar—NH
R_1R_2 = CHPh



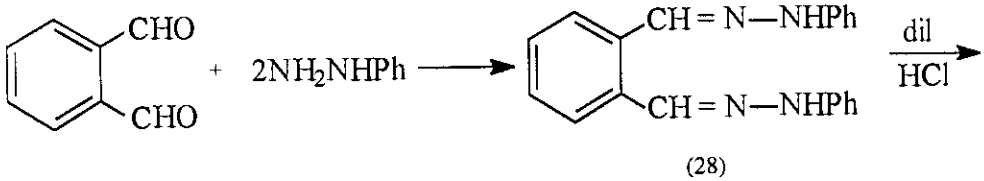
(25)

Methyl ester of 5-nitro homo phthalic acid (26) reacted with benzene diazonium chloride to yield phthalazinone ester (27) through hydrazone formation. Apparently the nitro group is essential for activation of the coupling reaction, since diethyl homophthalate failed to undergo the reaction[25-26].



(26) (27)

Also o-phthalaldehyde was treated with hydrazine derivatives to form bis hydrazone (28) which on partial hydrolysis with dilute hydrochloric acid gave 2-phenyl-1-hydroxy-1,2-dihydrophthalazine (29). The latter when was treated with $KMnO_4$ oxidized to 2-phenyl phthalazinone (30)[27].



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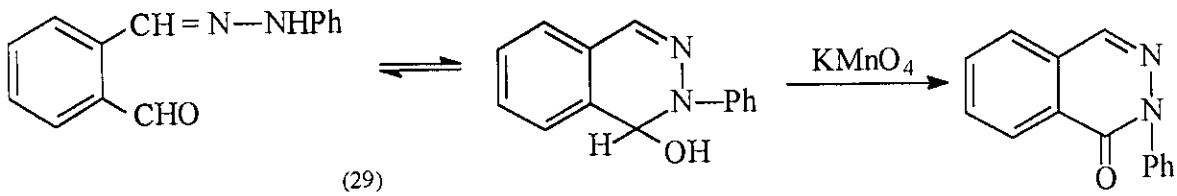
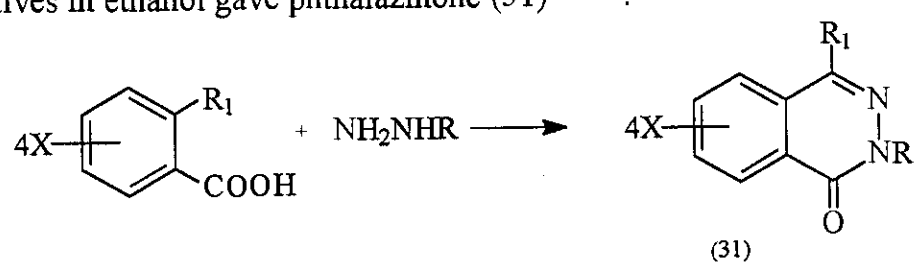


(29) (30)

(5) Benzoic acid derivatives

2-(Substituted)-3,4,5,6-tetrahalo benzoic acid when refluxed with hydrazine derivatives in ethanol gave phthalazinone (31) [28,29].



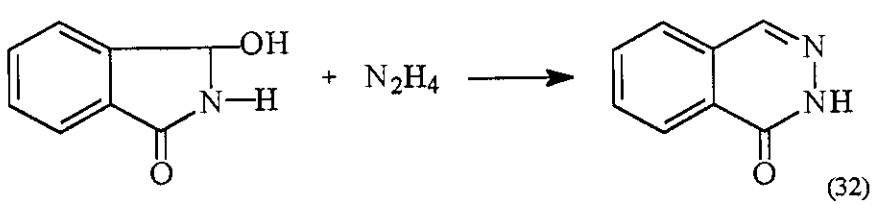
(31)

X = Cl, Br
R_1 = 2, 4-$Me_2C_6H_3$

R = H, Ph, $CONH_2$
COOEt

(6) Isoindolin-1-ones

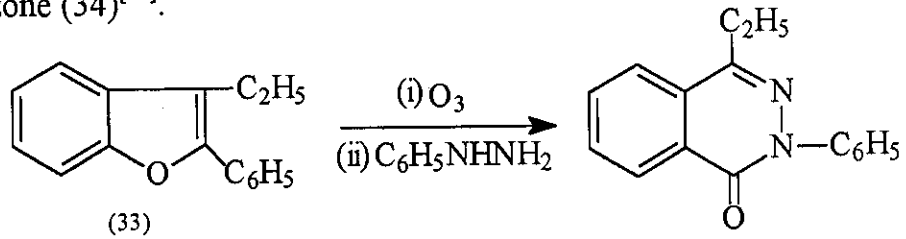
3-Hydroxy isoindolin-1-one reacted with hydrazine hydrate to give phthalazin-1-one (32) [30].



(32)

(7) Indenone derivatives

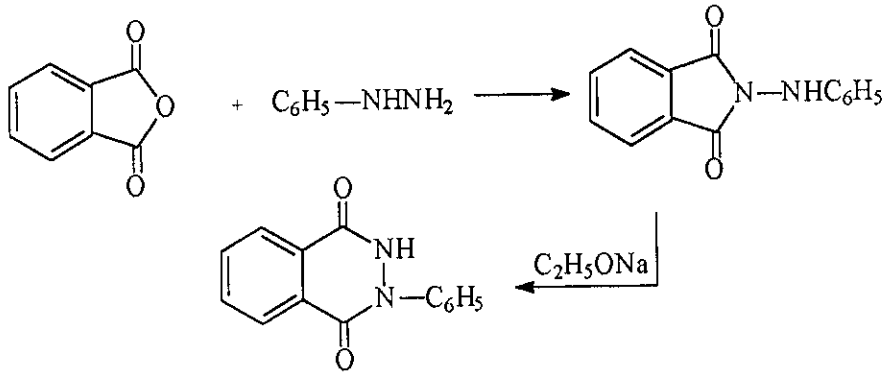
Ozonolysis of 2-phenyl-3-ethylindenone (33) gave stable crystalline ozonide which when treated with phenyl hydrazine gave 2-phenyl-4-ethyl phthalazone (34)[31].



(33) (34)

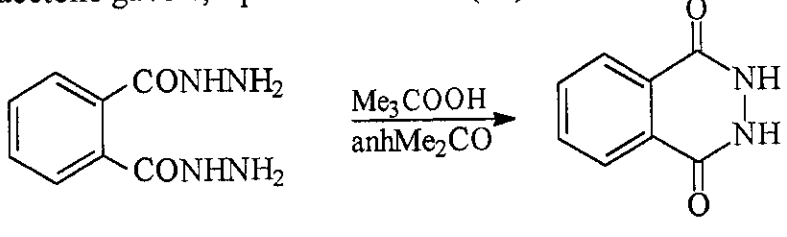
Synthesis of phthalazindiones was also described. The following are some examples for their synthesis.

Phthalic anhydride, dialkylphthalate and disodium phthalate were refluxed with an equimolar amount of phenyl hydrazine in ethanol to yield N-anilino phthalimide, which in turn was rearranged with sod. ethoxide to N-phenyl phthalazindione (35)[32,34].



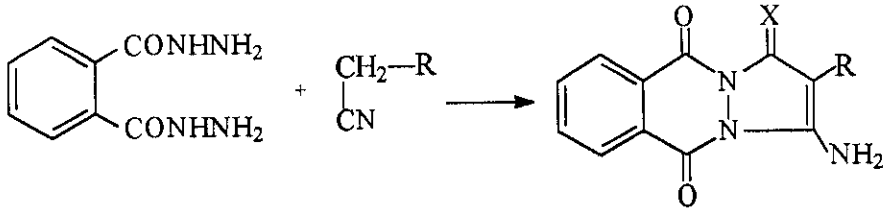
(35)

Also phthalhydrazide is an important precursor for the synthesis of phthalazindione. Thus oxidation of phthalhyhydrazide with $(CH_3)_3COOH$ in anhydrous acetone gave 1,4-phthalazindione (36)[35].



(36)

When phthalhydrazide reacted with malononitrile or cyanoacetate, it afforded the pyrazolophthalazine (37)[36] that has diverse applications as it coupled to form azo compounds.



(37)

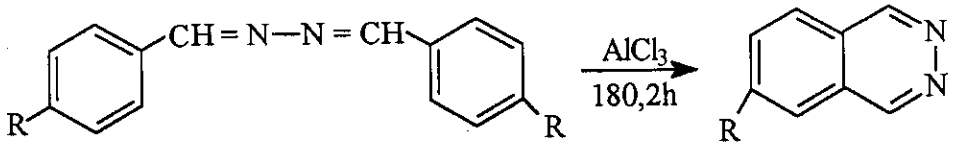
R = H, X = O, NH

Synthesis of Phthalazine:

Phthalazine derivatives also have a great potential in organic synthesis. Some of the most common method for their synthesis are illustrated below from:

(1) Aldazine

Heating of N,N-bis (4-isobutylbenzylidene) hydrazine (38) with $AlCl_3$ in o-dichlorobenzene at 180 °C for 2 hours gave 66% 6-isobutyl phthalazine (39)[37].

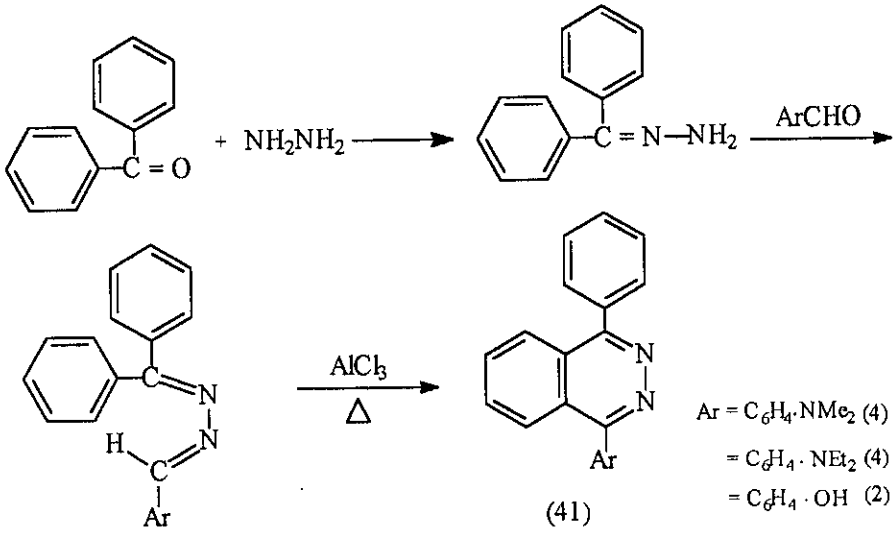


(38) (39)

R = isobutyl

(2) Aromatic ketones

Condensation of aromatic ketones such as benzophenone with hydrazine followed by condensation with aromatic aldehydes gave benzylidene benzophenone hydrazone (40). At elevated temperature (40) reacted with $AlCl_3$ to give the condensation product phthalazine (41)[38,39].



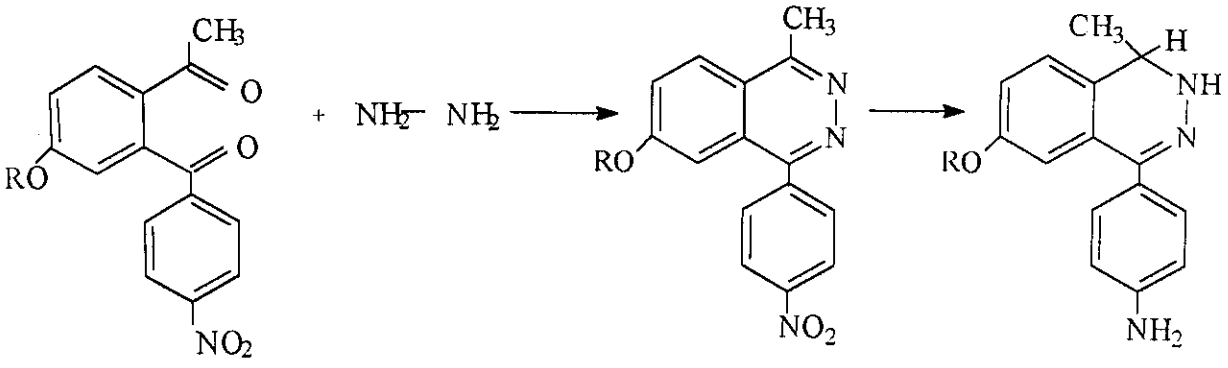
(40) (41)

Ar = $C_6H_4 \cdot NMe_2$ (4)

= $C_6H_4 \cdot NEt_2$ (4)

= $C_6H_4 \cdot OH$ (2)

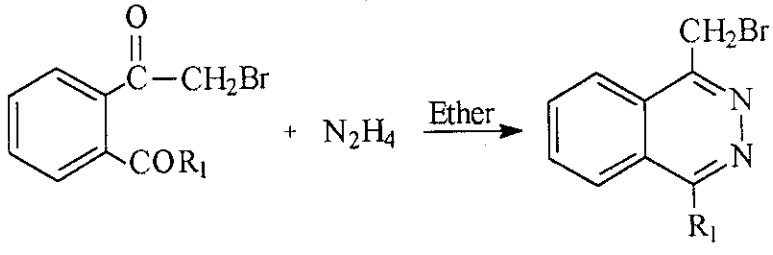
Also-4-methoxy-2-(4-nitrobenzoyl)acetophenone was cyclized with hydrazine and the product was reduced to phthalazine (42)[40].



(42)

R = alkyl

Treatment of o-bromoacetyl acylphenone with hydrazine hydrate in ether at 20 °C represents a simple and useful route to prepare 1,4-disubstituted phthalazine derivatives (43) in good yield[41].

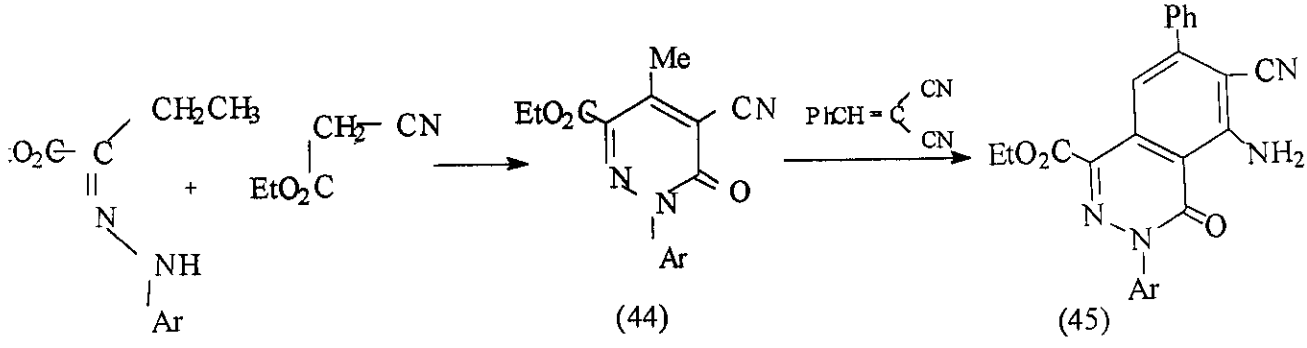


R_1 = Ph, Me

(43)

(3) Substituted pyridazine

Condensation of ethyl-2-aryl hydrazone-3-oxo-butyrate with active methylene nitriles gave 5-alkyl-3-oxo-2-phenyl pyridazin carbonitrile (44). The fused aryl ring was constructed via cyclo addition between (44) and arylidenemalononitrile to give poly substituted phthalazine (45)[42-45].



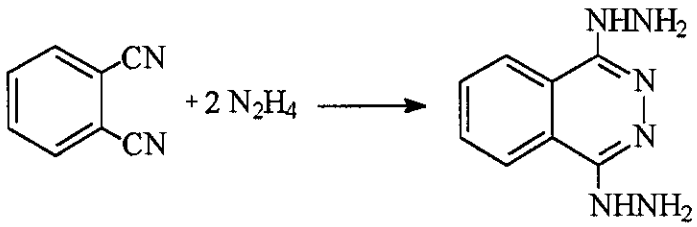
(44)

(45)

Ar = C_6H_4.Br

(4) Nitriles

Finally, 1,4-dihydrazinophthalazine (46) was synthesized from reaction of aquous hydrazine with phthalonitrile at 343-383 k in the presence of urea[46].



(46)

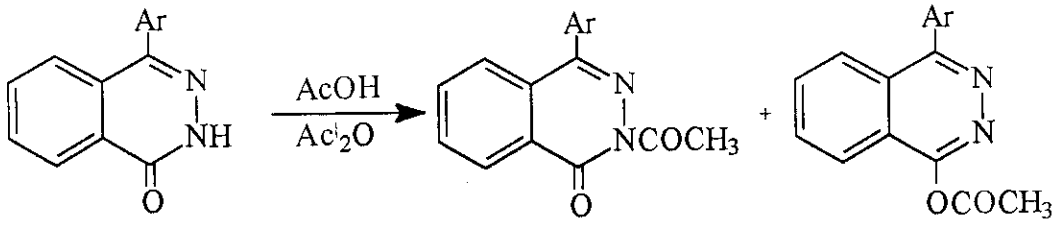
Reactions of 1(2H)-phthalazinones

Phthalazinone nucleus has a great potential in organic synthesis because of the presence of NH and OH functional groups.

(1) Alkylation and acylation

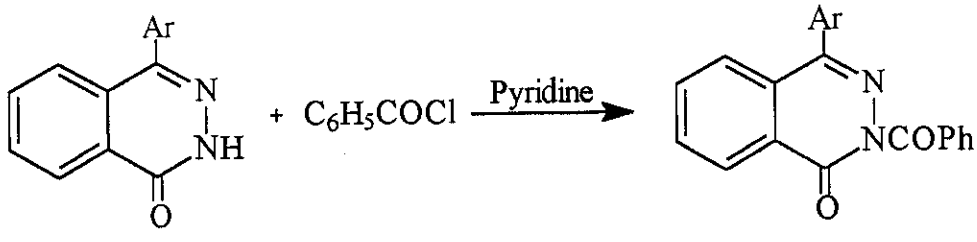
It was interesting to investigate the possibility of alkylation and acylation of phthalazinone at the OH and NH groups under different conditions[47].

Thus, acylation of the phthalazinone derivatives using acetic acid /acetic anhydride mixture gave two products identified as 2N-acetyl-4 (substituted)-1-(2H) phthalazinone and 1-acetoxy-4-(sub) phthalazine (47a,b)[14].



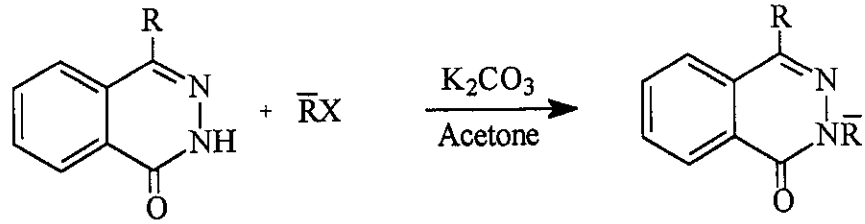
Ar = C_6H_5·C_6H_4 (47a) (47b)

Also phthalazinone reacted with benzoylchloride and pyridine to give 2-benzoyl phthalazinone (48)[48].



Ar = 4-Cl. 3-Me.C_6H_3 (48)

On the other hand alkylation of phthalazinone derivatives with a variety of electrophiles namely, dimethyl sulphate, ethyl chloro acetate, ethylchloro formate, aryl-alkylhalide and aryl sulphonyl halides in dry acetone in presence of anhydrous potassium carbonate, gave the corresponding 2-(substituted) phthalazinone derivatives (49)[48-51].

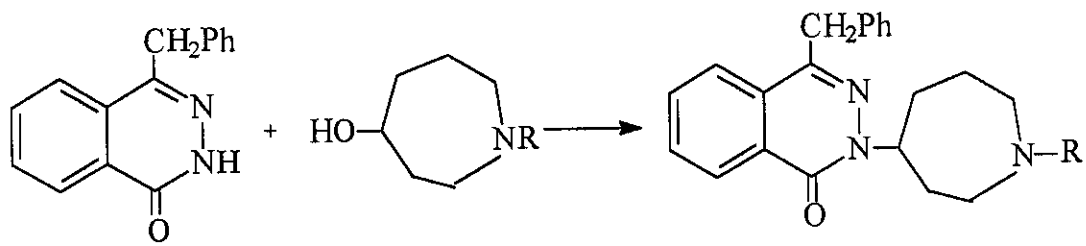


(49)

R = CH_3, 4-Cl.3-MeC_6H_3
$C_6H_4 \cdot C_6H_5$

$\bar{R}$ = CH_2COOEt, COOEt
$CH_2C_6H_4 \cdot CH_3$ *(p)*, $SO_2C_6H_5$
$SO_2 \cdot C_6H_4 \cdot CH_3$ *(p)*.

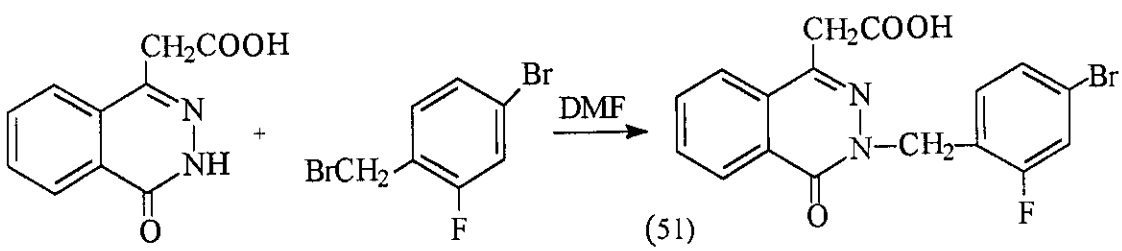
Treatment of benzyl phthalazinones with homopiperazinol in the presence of dehydrating-condensating agent afforded 2-(sub.)-phthalazinones which are known as antihistaminics (50)[52].



R = CH_3

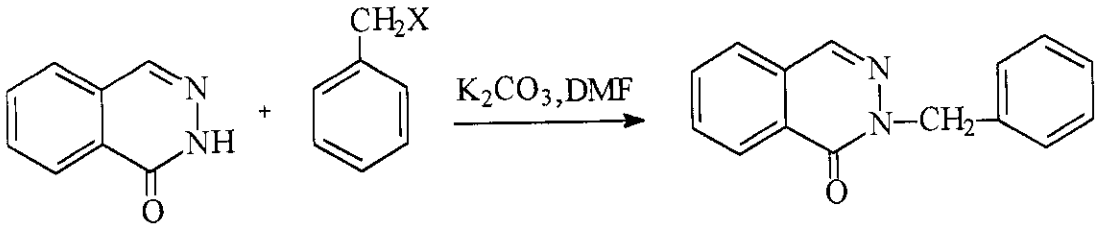
(50)

3,4-Dihydro-4-oxo-1-phthalazine acetic acid in anhydrus DMF was added to $Me_4N^+OH^-$. The resulted solution was then treated with 4,2-BrF $C_6H_3CH_2Br$ in PhCl to give 3-[(4-bromo-2--flurophenyl) methyl]-3,4-dihydro-4-oxo-1-phthalazine acetic acid (51) in 94% yield[53]. This compound is used for treatment of diabetes.



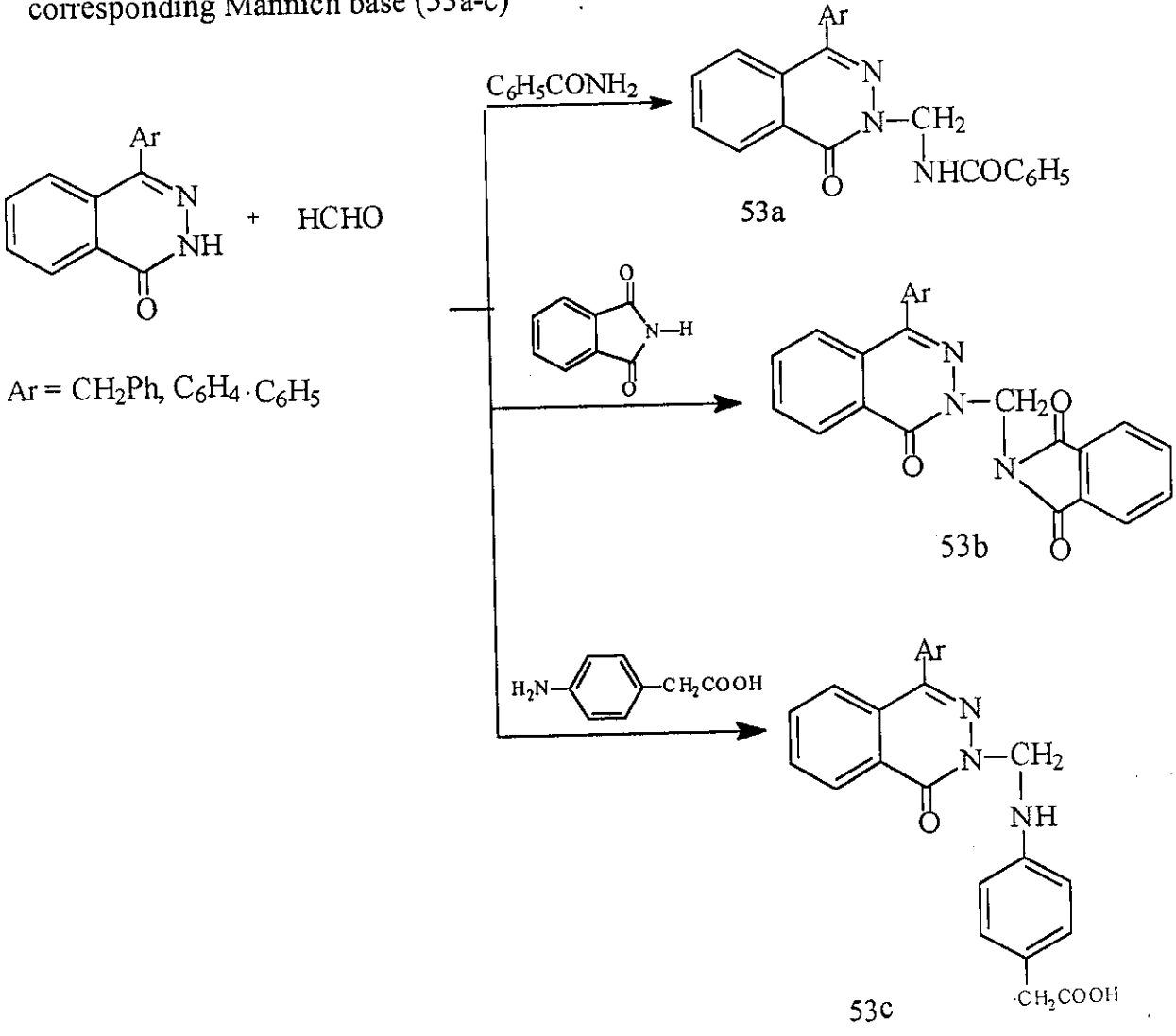
(51)

Similarly microwave irradiation of 1(2H)-phthalazinone with benzyl halides and potassium carbonate in DMF afforded the 2-benzyl-1(2H) phthalazinones (52) in modest yield. The majority of the products exhibited anticonvuslant protection[54].



(52)

Phthalazinone derivatives reacted with benzamide, phthalimide and *p*-amino phenylacetic acid in the presence of formaldhyde in methanol. The reaction mixture was refluxed for an appropriate time to give the corresponding Mannich base (53a-c)[14, 55].



Ar = CH_2Ph, $C_6H_4 \cdot C_6H_5$

53a

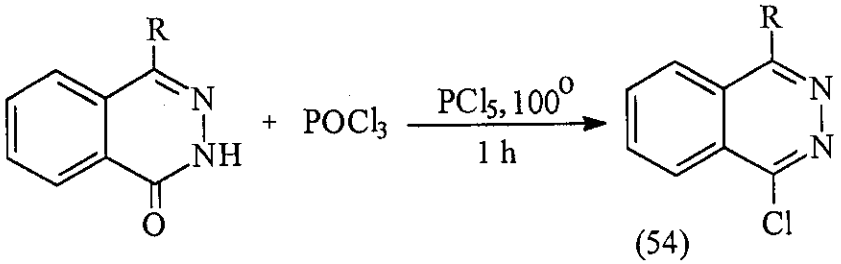
53b

53c

(2) Reactions at the side chain

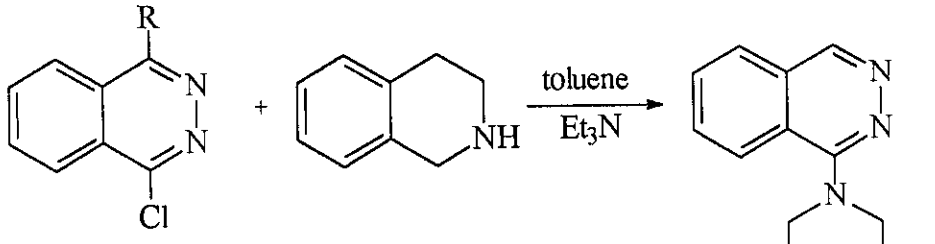
a- Reaction with chloro atom

Chlorination of phthalazinone derivatives with phosphorus oxychloride in presence of PCl_5 at 100 °C for 1 hour afforded 1-chloro phthalazine (54)[51,56,57], which is the precursor for variety of phthalazine derivatives.



(54)

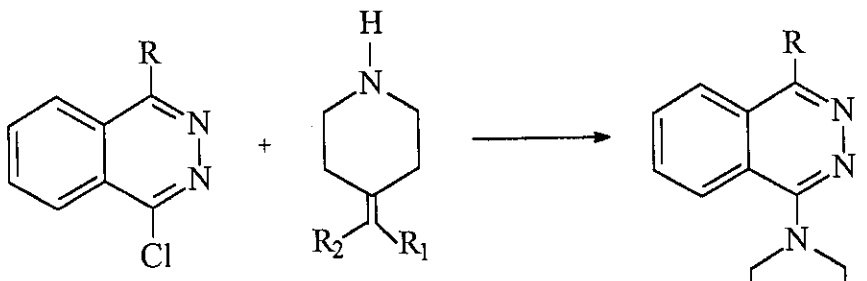
Thus, 1-chlorophthalazine derivatives were condensed with 1,2,3,4-tetrahydroisoquinoline in toluene in the presence of Et_3N under reflux for 16 h to give 1-(1,2,3,4-tetrahydroisoquinolin-2-yl)phthalazine (55)[57].



R = H, Substituted alkyl or aryl

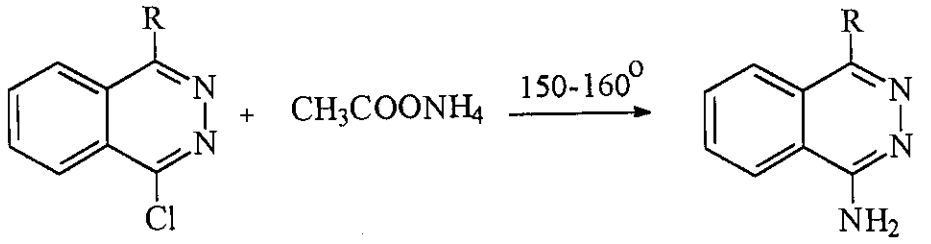
(55)

1-chlorophthalazine derivative reacted with 4-(2-dithienylmethylene) piperidine and with ammonium acetate at 150-160 °C for 30 min to prepare piperidinyl phthalazine (56)[58] and aminophthalazine (57)[59] respectively.



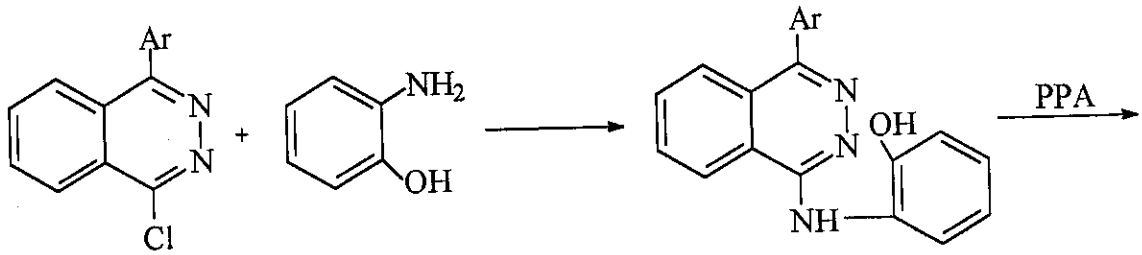
$R_1 = R_2 =$2-thienyl

(56)



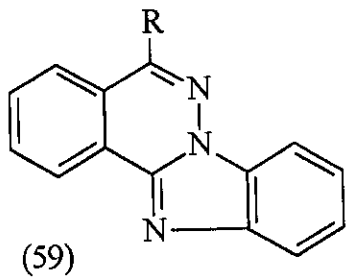
(57)

Treatment of 1-chlorophthalazine derivatives with 2-amino phenol gave 1-N-(2-hydroxyphenyl)amino-4-substitutedphthalazine (58).Cyclo dehydration of (58) employing PPA gave benzimidazolo[2,3-a] phthalazine(59)[60] which has antiinflammatory and antihypertensive activities.



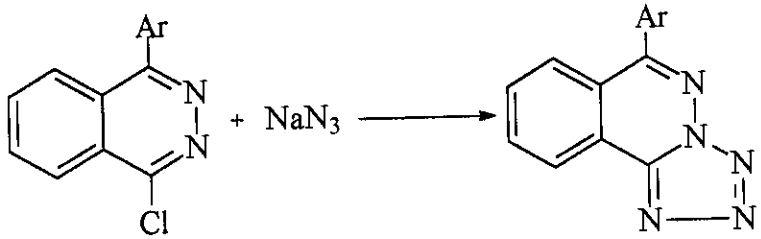
(58)

Ar = C_6H_5, 4-Cl.C_6H_4, 4-Me.C_6H_4



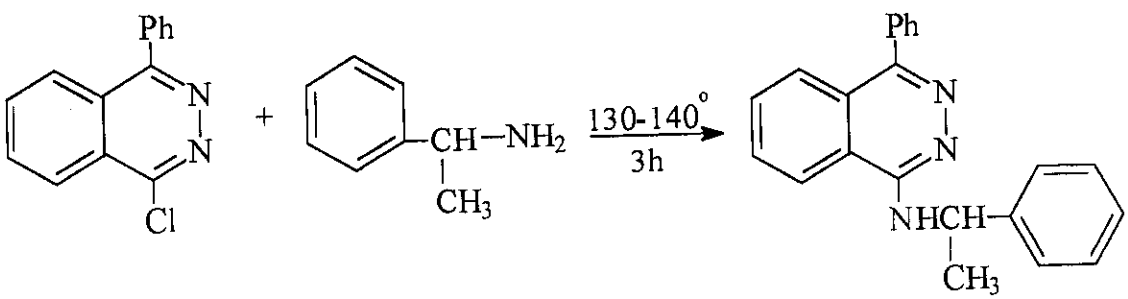
(59)

Sodium azide reacted with 1-chlorophthalazine derivatives to form tetrazolophthalazine (60)[61].



(60)

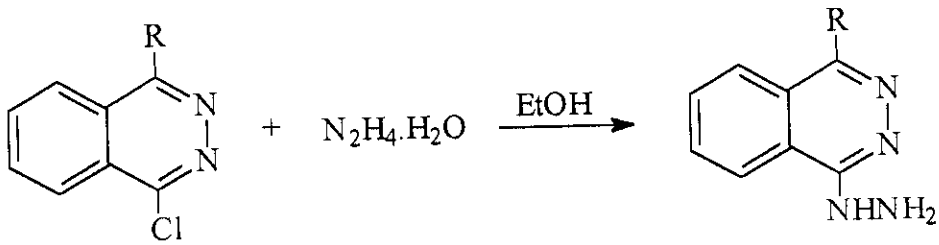
D-α-methylbenzylamine was treated with 1-chloro-4-phenyl phthalazine for 3h at 130-140 °C to give 1-benzylamino-4-phenyl phthalazine (61)[62].



(61)

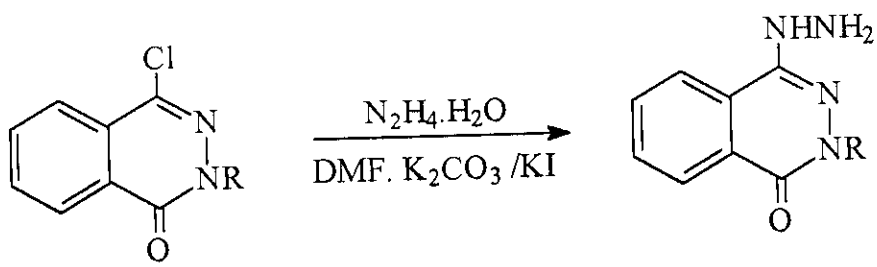
b- Reactions with hydrazine group

Treatment of 1-chloro-4-sub.phthalazine with hydrazine hydrate in absolute ethanol or benzene gave the corresponding 1-hydrazino-4-substituted phthalazine (62)[48,50].



(62)

On the other hand, 4-hydrazino-1(2H) phthalazone (63) can be prepared from the reaction of the corresponding 4-chloro-1(2H) phthalazinone with N_2H_4 in DMF [63].

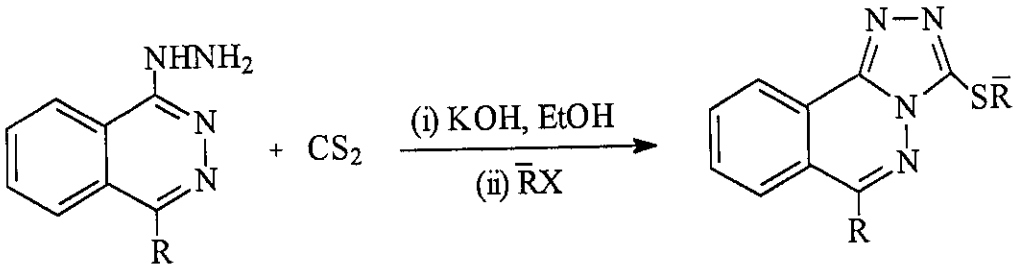


(63)

Hydrazinophthalazines were found to have diverse applications both biologically and in organic synthesis.

Thus, recent investigation had demonstrated significant bilogical activity of hydrazino phthalazines (hydralazines) and their usage as antihypertensive agents[64]. They were also considered as important intermediates for synthesis of different heterocyclic compounds as follows:

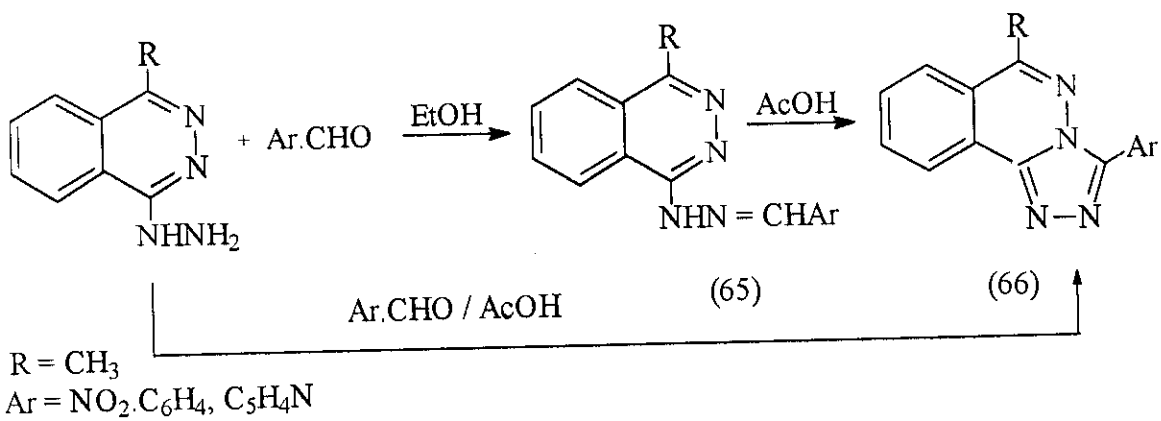
(i) Triazoles, hydrazinophthalazine derivatives are considered to be good precursor for triazoles. Thus hydrazino phthalazine was refluxed with carbon disulfide in chloroform or in KOH and ethanol to give *s*-triazolo [3,4-a] phthalazin-3- thiol which reacted with alkyl halide to afford the corresponding sulfide (64)[50,65].



(64)

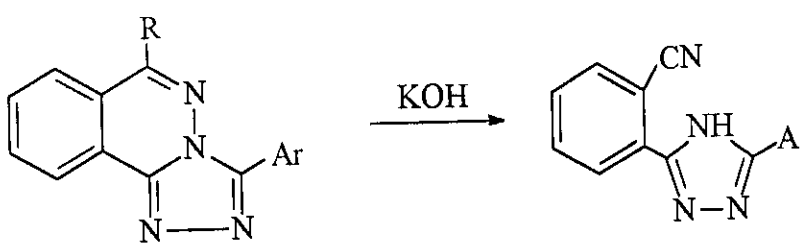
Condensation of hydrazinophthalazine with aromatic aldehydes in absolute ethanol gave the corresponding N-arylidene hydrazone (65), which was then refluxed with acetic acid to give triazole (66) [50,66].

Triazole (66) can be obtained directly from condensation of hydrazinophthalazine with aromatic aldehydes in acetic acids[50].



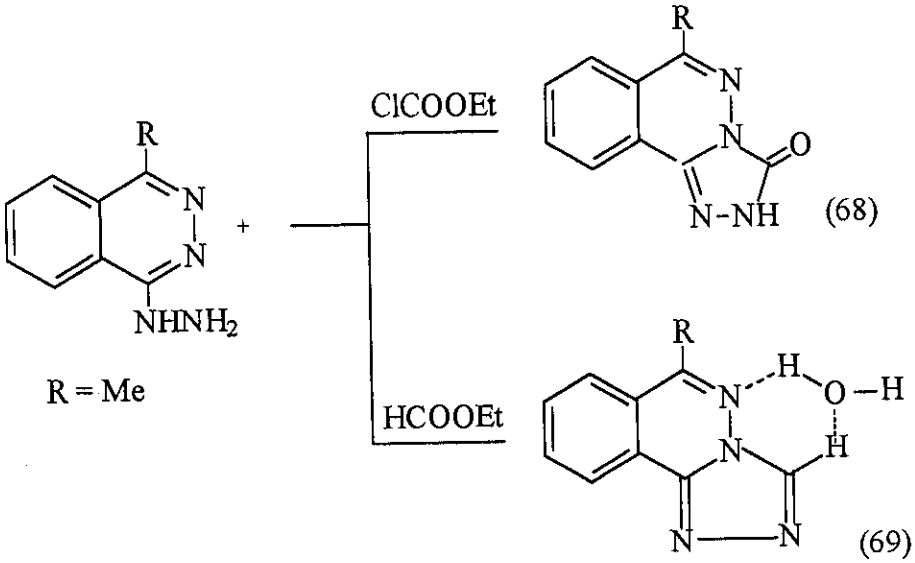
R = CH_3
Ar = $NO_2.C_6H_4$, C_5H_4N

S-triazolo-[3,4-a]- phthalazine (66) underwent ring opening by action of KOH / alcohol or aquous NaOH to give 3-(2-cyanophenyl)-*s*-triazole (67) [65].

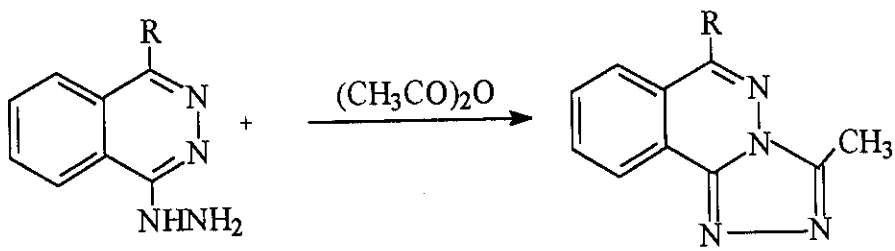


(66) (67)

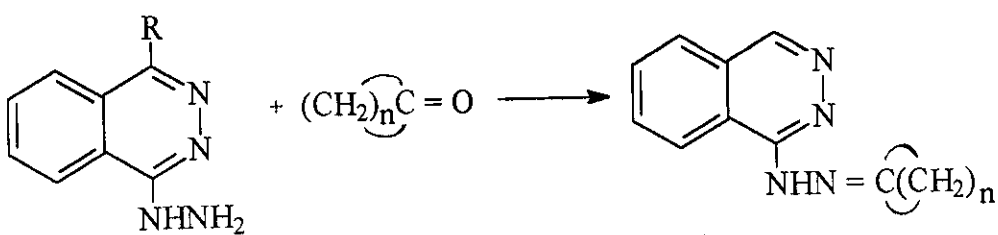
Reaction of 1-hydrazinophthalazine with carbonyl compounds e.g. ethyl chloro formate in pyridine at 100 °C, ethyl formate in absolute ethanol gave triazolo [3,4-a]-6-(sub.)phthalazine-3-one (68) and *s*-triazolo [3,4-a]-6-(sub.)phthalazine hydrate (69) respectively [50,67].

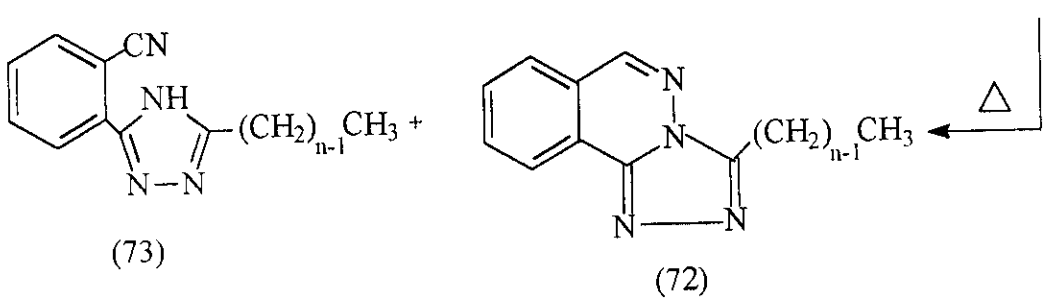


Refluxing hydrazinophthalazine in acetic anhydride gave 75% of 3-methyl-s-triazolo[3,4-a]-6-(sub.)phthalazine (70)[50].

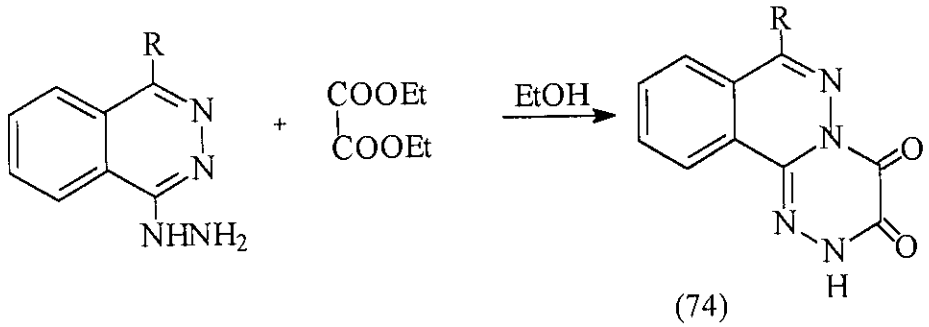


Also hydrazinophthalazine reacted with cycloalkanone in acetic acid to give hydralazone derivatives (71)[68] which were separated by column chromatography.Pyrolysis of the isolated product under nitrogen atm. at 250 °C for 1 hour gave a mixture of two products identified as (72,73).



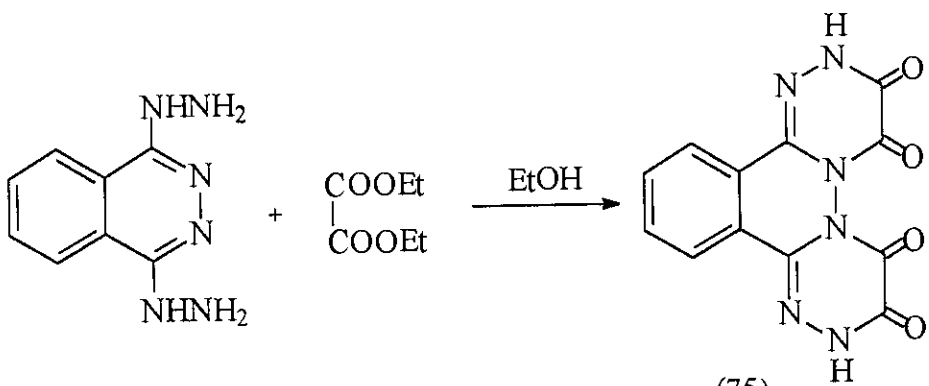


(ii) Triazine, hydrazinophthalazine reacted with diethyloxalate in absolute ethanol to give 2H *as* triazino [3,4-a] 7-methyl phthalazine-3,4-dione (74)[50,69].



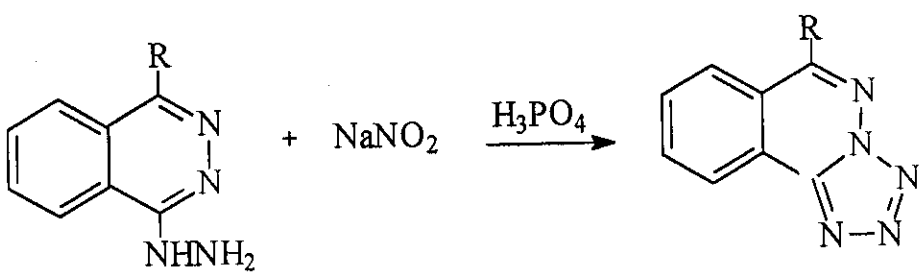
(74)

Likewise the reaction of 1,4-dihydrazinophthalazine with diethyl oxalate afforded bis-1,2,4-triazinophthalazine(75)[70].



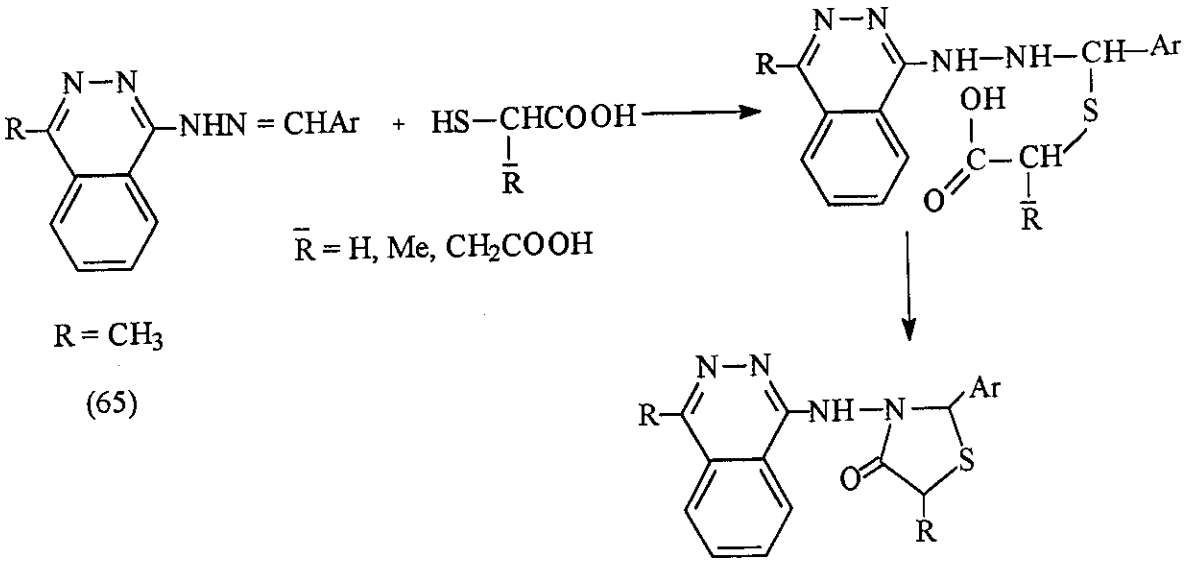
(75)

(iii) Tetrazole derivatives were also derived from hydrazinophthalazine. Thus, when hydrazinophthalazine reacted with sod nitrite and H_3PO_4, tetrazolo [5,1-a] phthalazine (76)[50] was obtained.



(76)

(iv) Cyclocondensation of N-arylidenehydrazone (65) with carboxylic acid thiol gave (thiazolidinone-3-yl) amino phthalazine (77)[71].

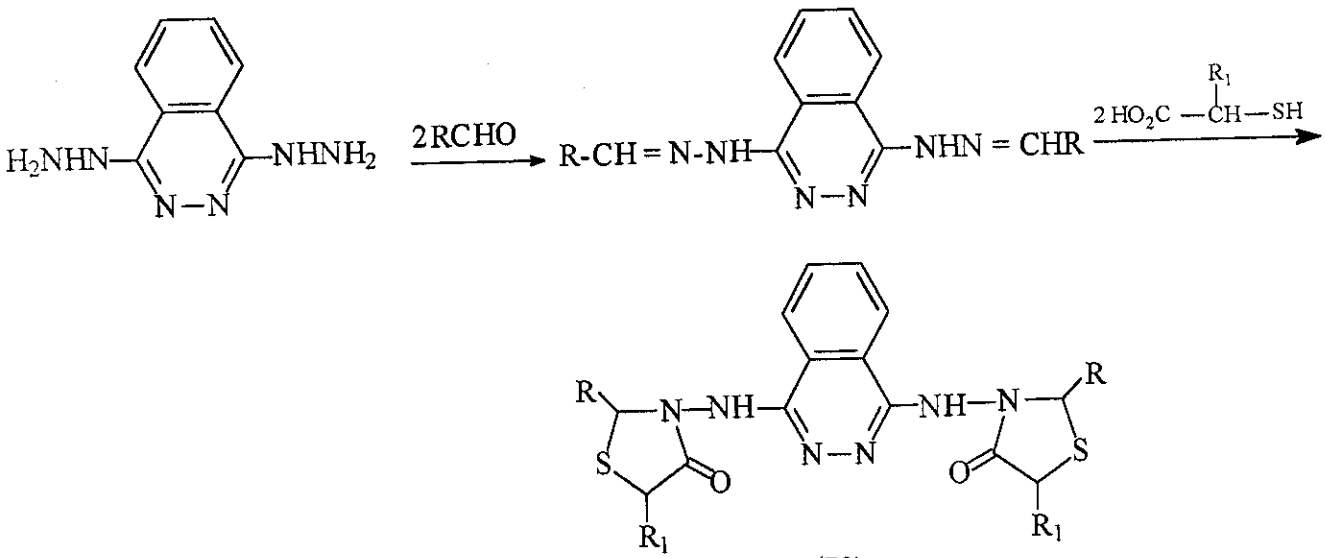


$R = CH_3$

(65)

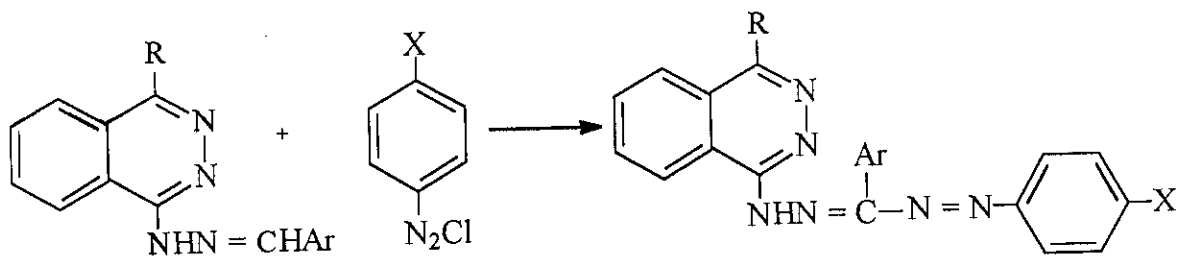
(77)

Similarly, condensation of 1,4-dihydrazinophthalazine with aromatic aldehydes followed by cyclization with mercapto acetic acid gave bis-(thiazolidinonyl-amino) phthalazine (78)[72-73].



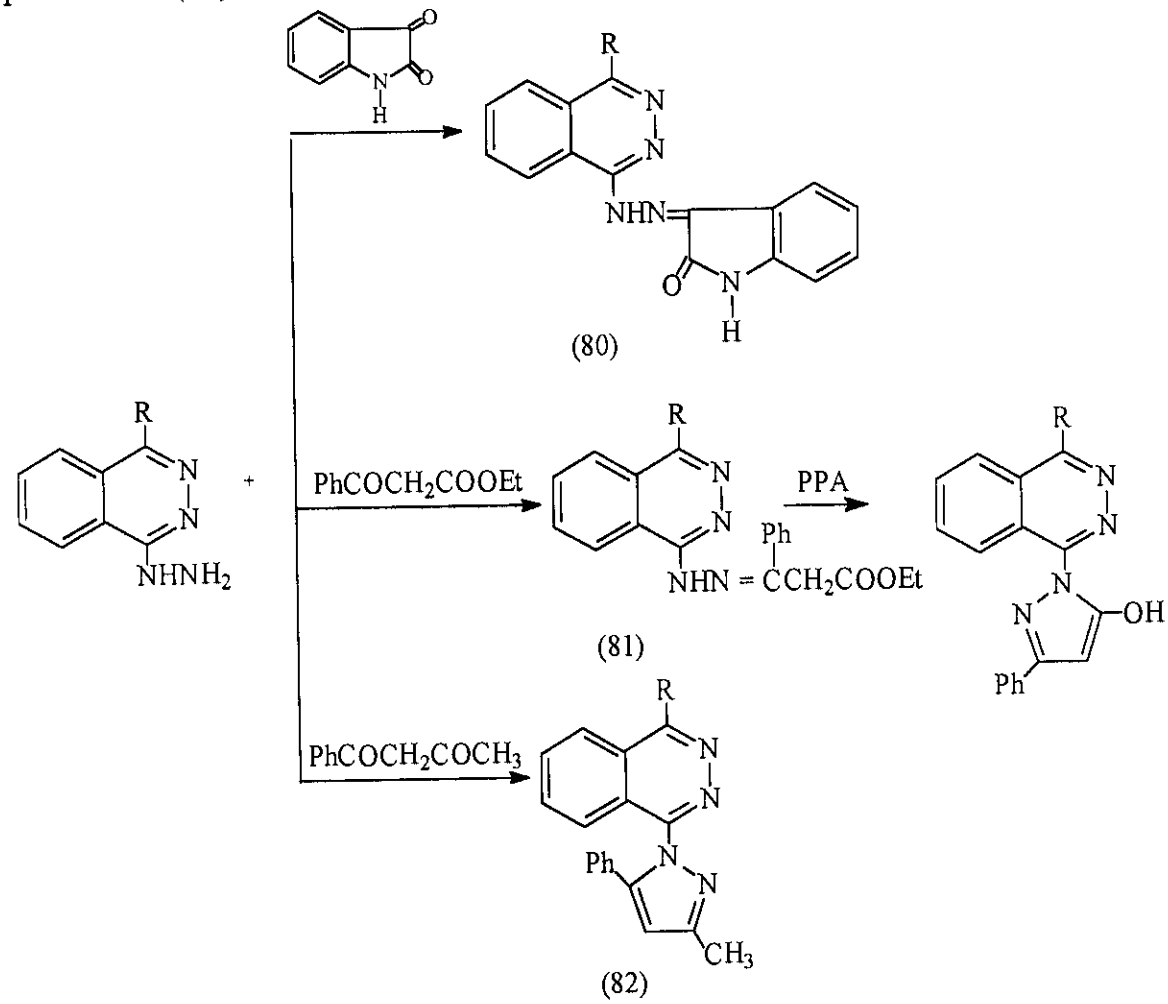
(78)

(v) Also N-arylidenehydrazone (65) reacted with arenediazonium salts forming 1-[α-(*p*-sub.phenylazo)-sub.benzaldhyde] hydrazinophthalazine (79)[74].



(65) (79)

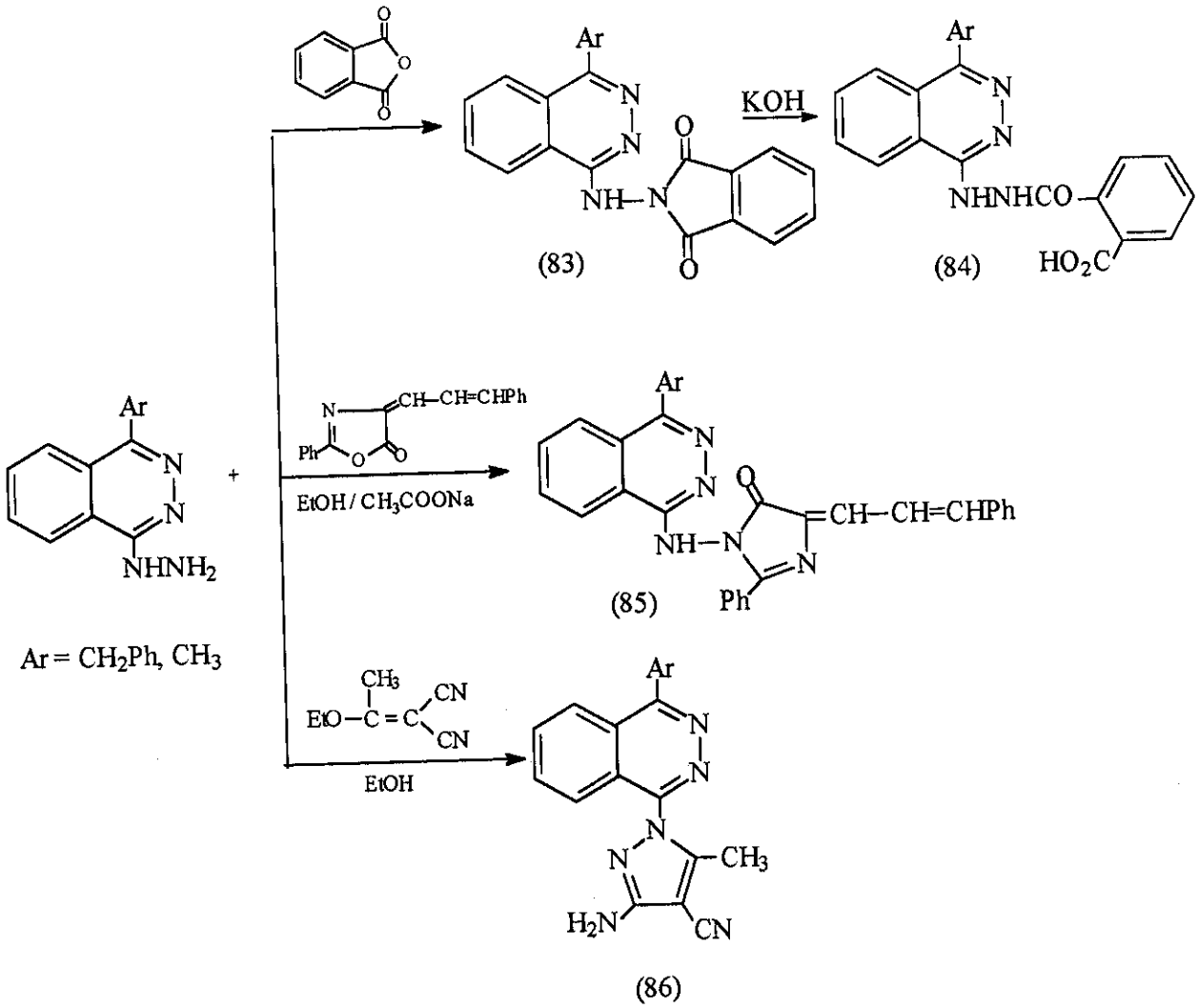
(vi) Hydrazinophthalazine reacted with dicarbonyl compounds derivatives such as indol-3,4-dione and benzoyl acetate in refluxing MeOH to give the corresponding hydrazone (80)[75], and (81)[76] respectively. However, when reacted with benzoyl acetone it afforded 1[3-methyl-5-phenyl pyrazolyl]-4-alkyl phthalazine (82)[76].



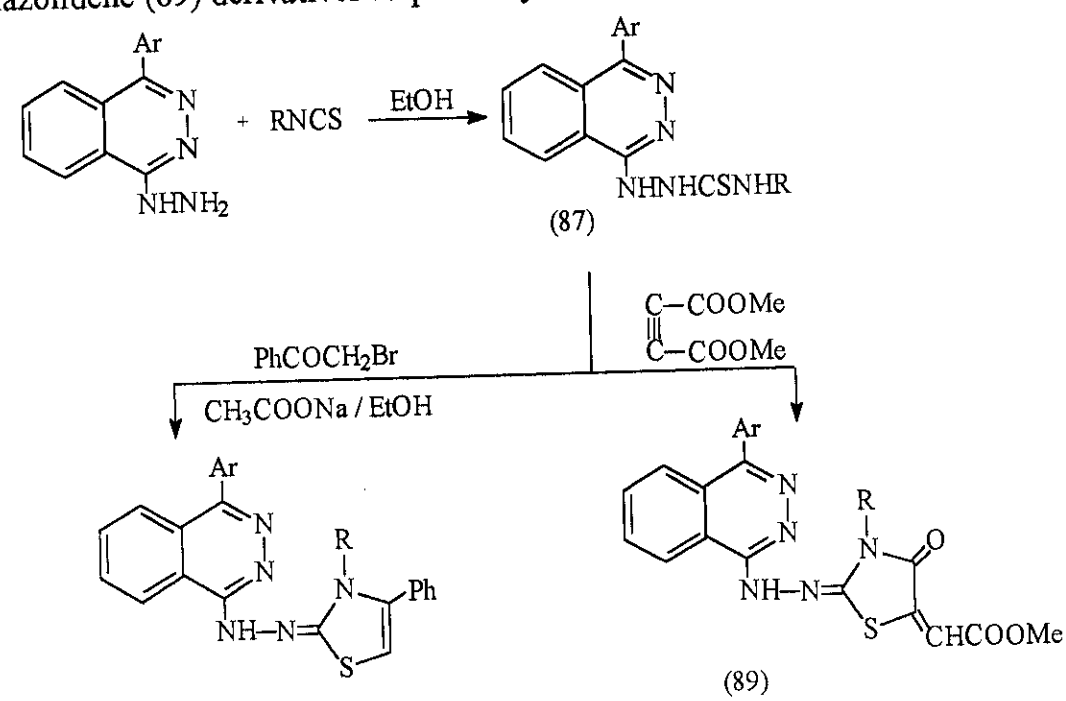
(80) (81) (82)

(vii) Hydrazinophthalazine derivatives reacted with phthalic anhydride in refluxing DMF for 2 h to give N-(1-amino-4-subphthalazine) phthalimide (83) which upon alkaline hydrolysis gave 4-substituted-1-(2-phthalayl hydrazino) phthalazine (84)[77].

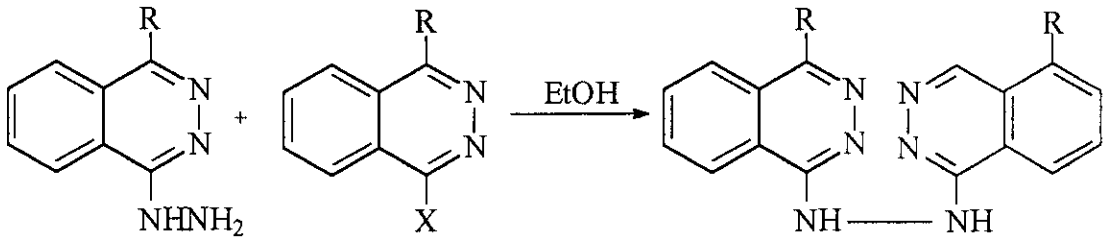
Also, hydrazinophthalazine reacted with 4-cinnamyliden-2 phenyl-oxazole-5-one and ethoxy ethylidene malanonitrile in refluxing ethanol to afford 1-(4-cinnamyliden-2-phenyl-2-imidazol-5-one-1-ylamino)-4-sub.phthalazine (85) and 1-(4-benzyl-1-phthalazinyl)-3-amino-4-cyano-5-methyl pyrazole (86), respectively[77].



(viii) Addition of alkyl or phenyl isothiocynate to hydrazinophthalazine in refluxing EtOH gave thiosemicarbazide (87)[77], which upon treatment with phenacylbromide and dimethylacetylene dicarboxylate gave thiazoline (88) and oxathiazolidene (89) derivatives respectively.



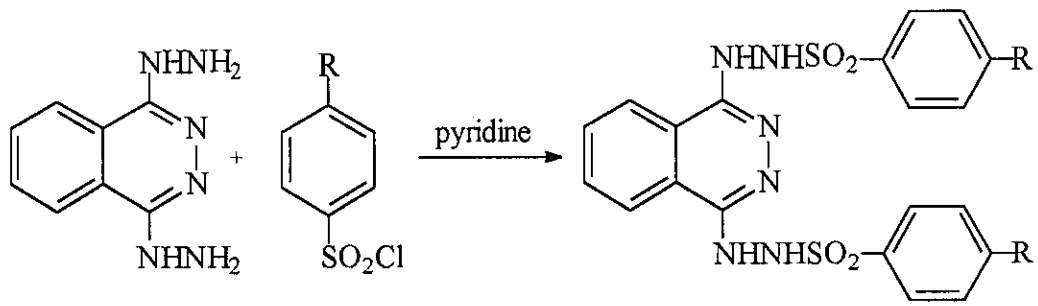
Treatment of 1-hydrazinophthalazine with 1-chlorophthalazine or phthalazinthione derivatives in absolute EtOH afforded 1,2-bis-(4-sub. phthalazinyl) hydrazide (90)[50].



X = Cl, SH

(90)

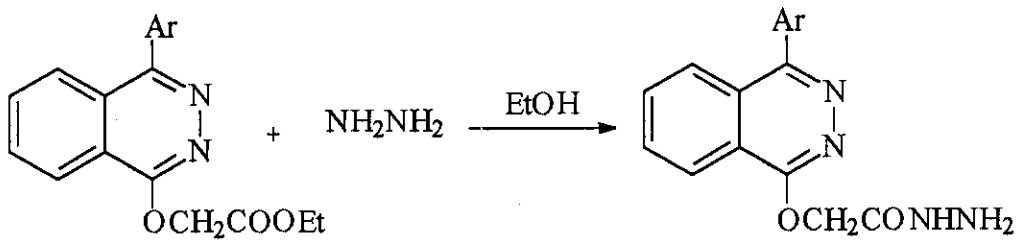
1,4-Dihydrazinophthalazine reacted with substituted acid sulphonyl chloride in pyridine to give bis (arylsulphonyl hydrazino)phthalazine (91)[78].



(91)

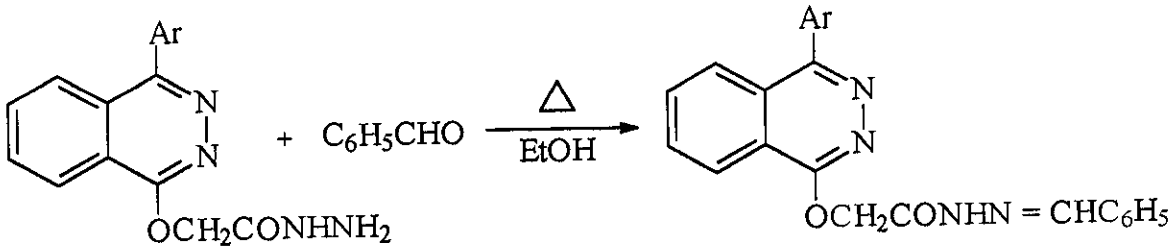
c- Reaction with acid hydrazide.

Oxyacid hydrazides (92) were prepared via the reaction of 1-(ethoxycarbonyl-methoxy)-4-sub.phthalazine with hydrazine hydrate or phenylhydrazine in absolute EtOH[14].



(92)

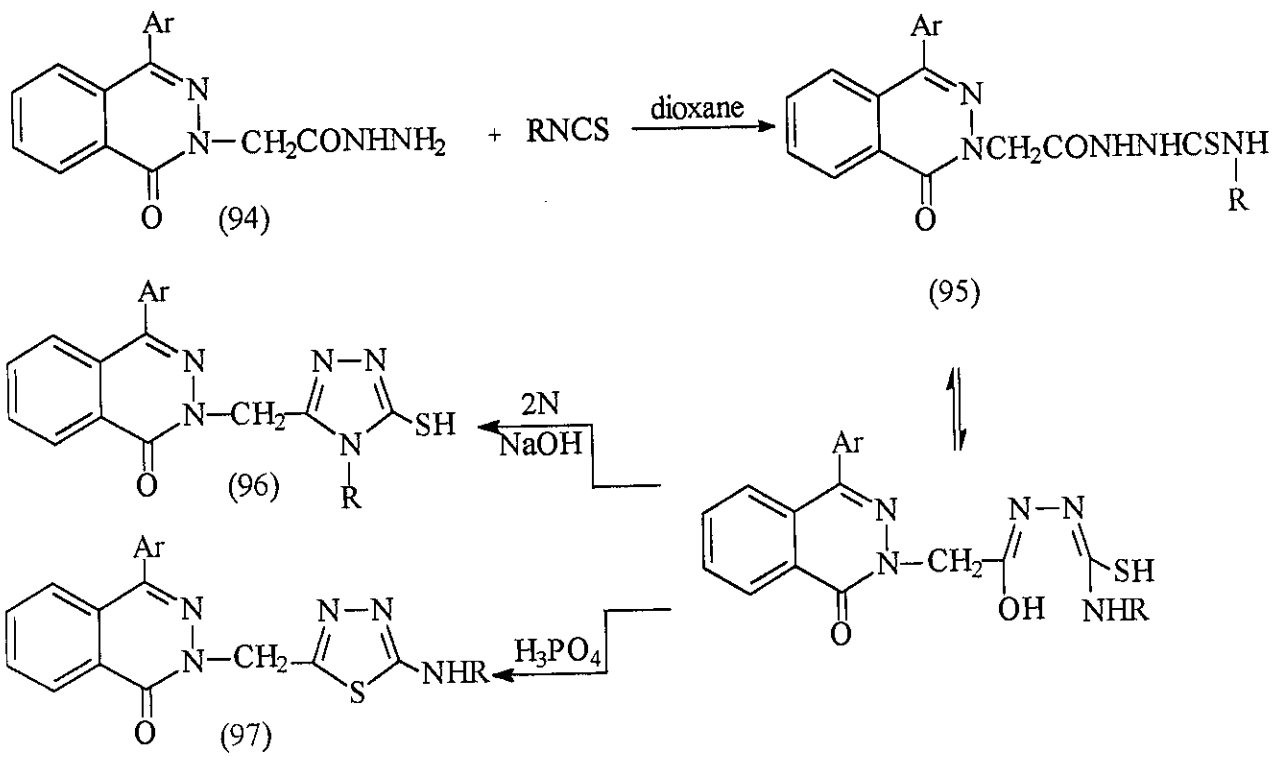
Acid hydrazide (92) reacted with benzaldhyde in boiling EtOH containing few drops of piperidine to give the corresponding Schiff's base (93)[14].



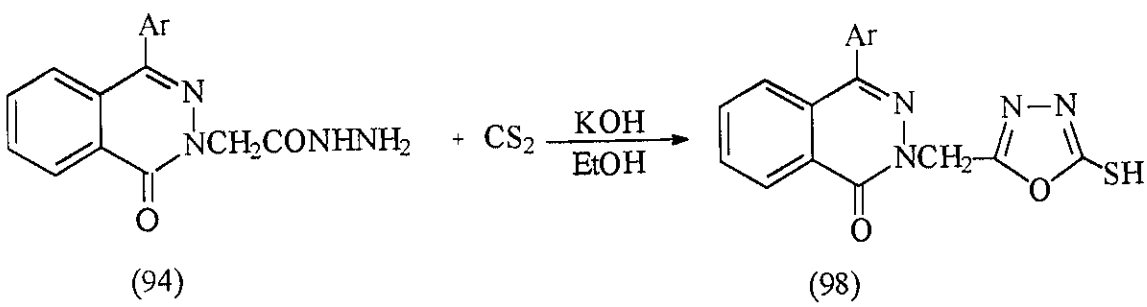
(93)

The acid hydrazide side chain underwent a variety of ring closure reactions. The following are few of the reported reactions.

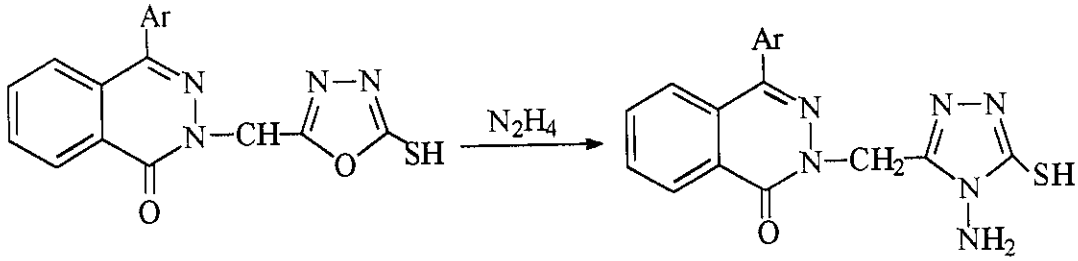
N-acid hydrazide (94) was allowed to react with different isothiocyanates in refluxing dioxane to give thiosemicarbazide (95), which was cyclized to produce a second heterocyclic nucleus. Thus treatment of (95) with NaOH and H_3PO_4 afforded *s*-trizolophthalazine (96) and thiadiazolophthalazine (97)[79].



On the other hand treatment of acid hydrazide (94) with carbon disulfide in EtOH/KOH gave oxadiazolophthalazinone (98)[80].



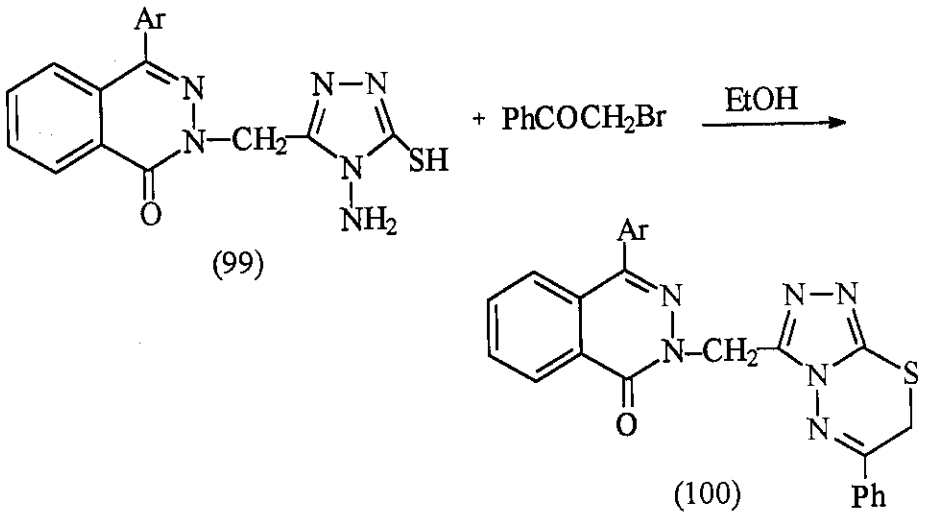
Subsequent treatment of oxadiazolophthalazinone (98) with hydrazine gave 2-[4-amino-5-mercapto-*s*-triazolo-3-yl-methyl]4-arylphthalazinone (99)[79].



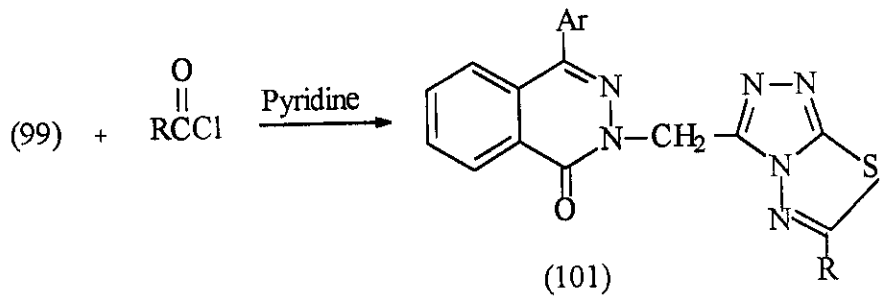
(98) (99)

The presence of the 4-amino and 5-mercaptosubstituents in the triazole ring furnished a new start for fused heterocyclic nucleus.

Thus, when triazolophthalazine (99) was condensed with phenacyl bromide in refluxing EtOH and with acid chloride in pyrdine, 2-(6-aryl-7H-*s*-triazolo-[3,4-b]-1,3,4-thiadiazin-3-yl-methyl)-4-sub.-1-(2H) phthalazinone (100) and 2-(6-aryl-*s*-triazolo-[3,4-b]-1,3,4-thiadiazol-3-yl-methyl)-4-sub.-1-(2H) phthalazinone (101) were formed respectively[79].

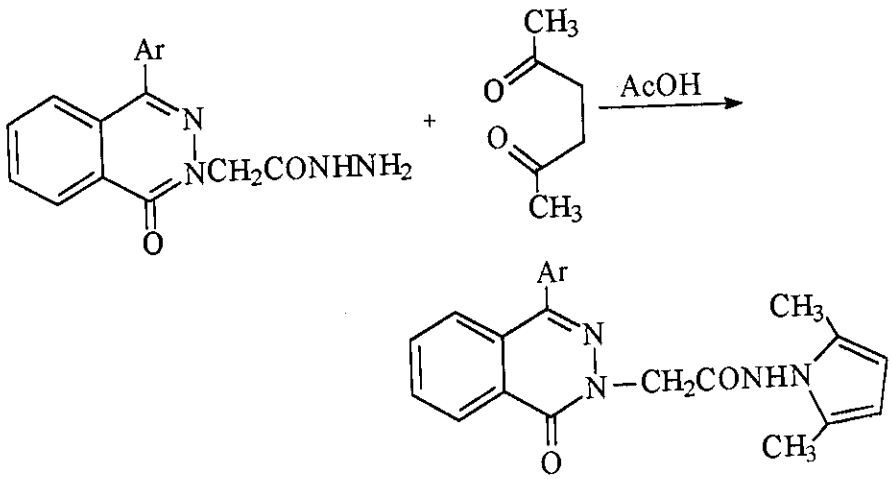


(99) (100)



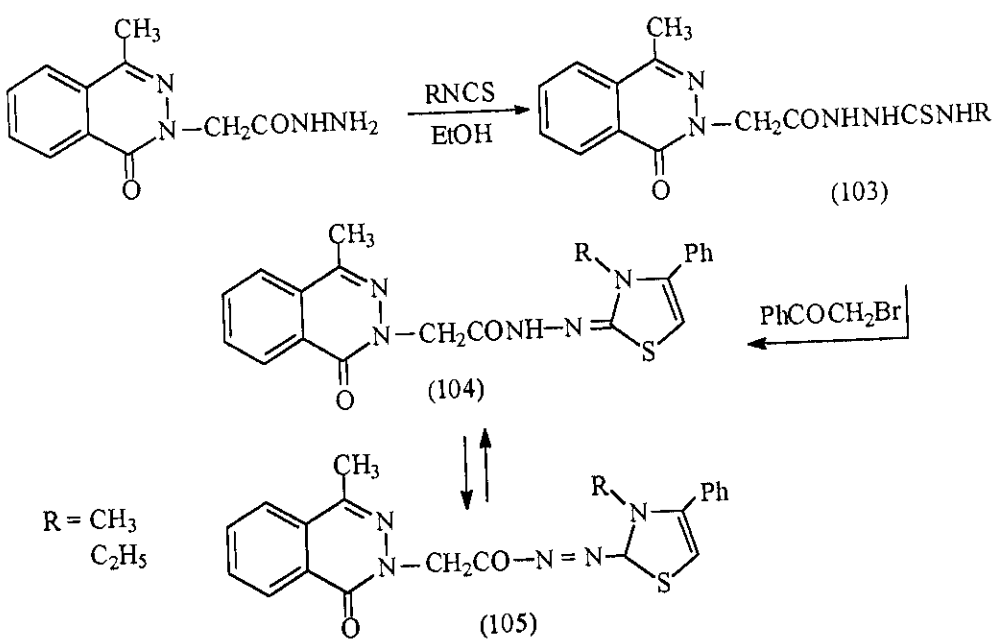
(101)

Further acid hydrazide (94) reacted with 2,5-hexanedione in glacial acetic acid to form 2-(2,5-dimethylpyrrole-1-yl-amino carbonylmethyl)-4-aryl-1(2H) phthalazinone (102)[79].



(102)

Treatment of acid hydrazide with isothiocyanate in alcoholic media gave thiosemicarbazide (103) which on condensation with phenacylbromide gave N-(4-methyl-1(2H)phthalazinone-2-yl-acetyl)-N-3,4-disub.2,3-dihydrothiazol-2-ylidene) hydrazine(104)[81] and the corresponding azo form (105).



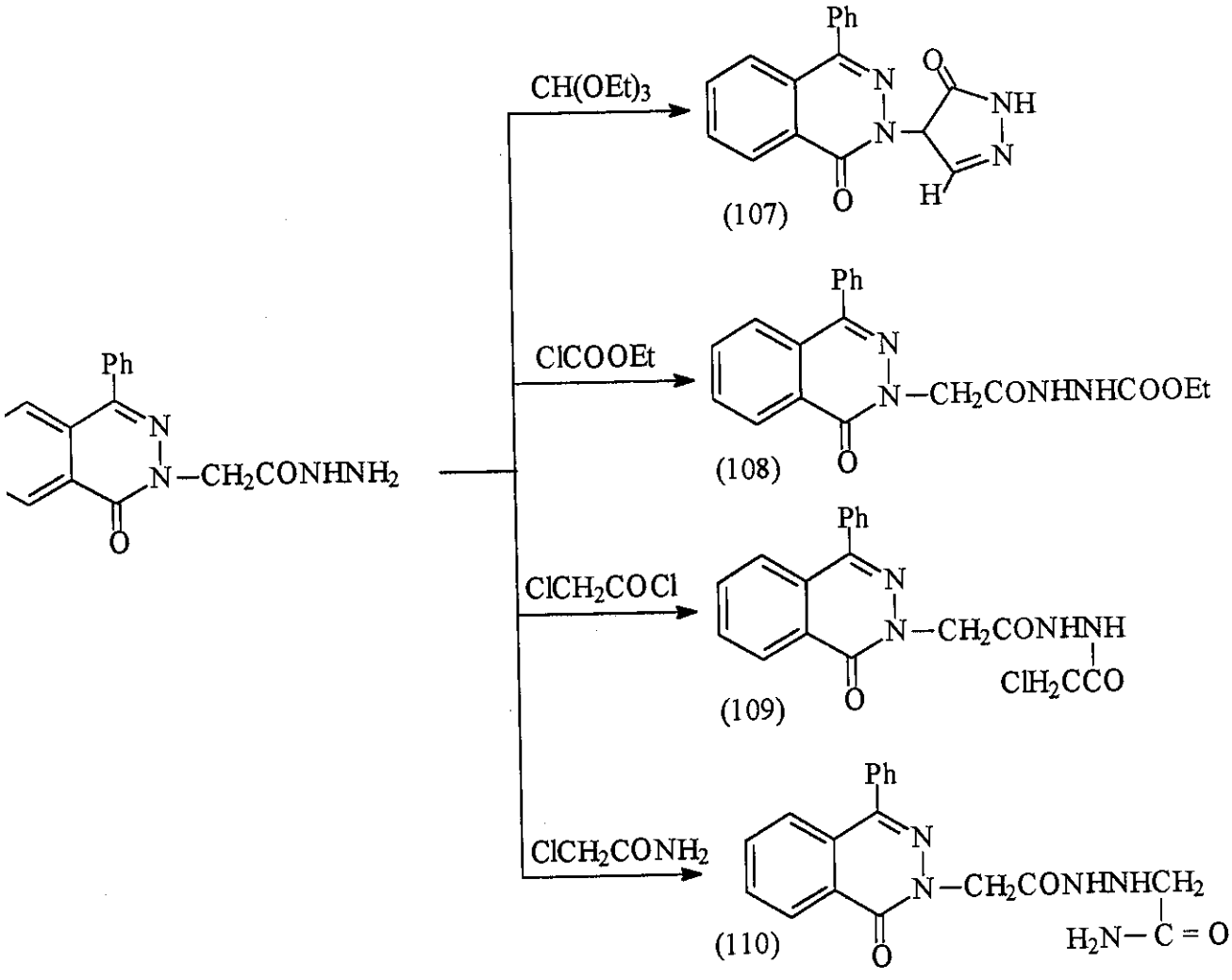
(103)

(104)

(105)

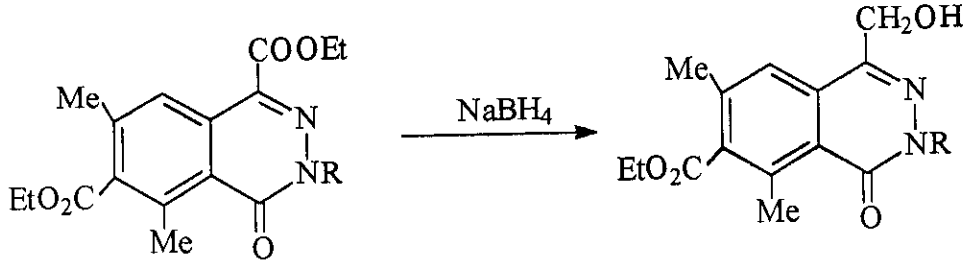
It was reported that condensation of acid hydrazide (106) with esters such as triethylorthoformate at reflux for 4 hours gave 70% phthalazinyl

pyrazolone (107)[82]. Also it reacted with halocompound such as ethyl chloroformate, chloroacetylchloride and chloroacetamide to give the corresponding carbethoxyhydrazide (108-110)[83].



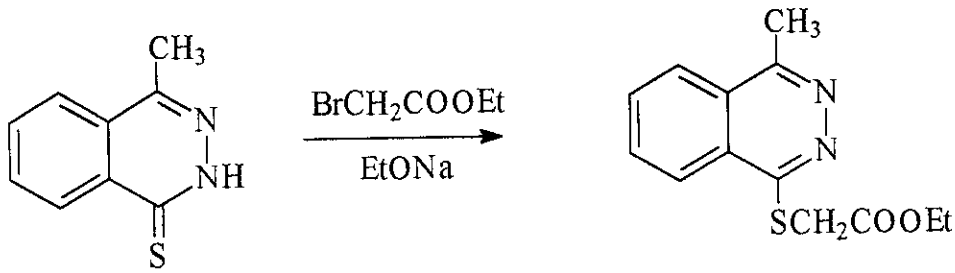
d- Reaction of ester group

7-Ethoxy carbonyl-6,8-dimethyl-4-hydroxymethyl-1(2H) phthalazinones (111) were prepared by reduction of their ester with $NaBH_4$[23].



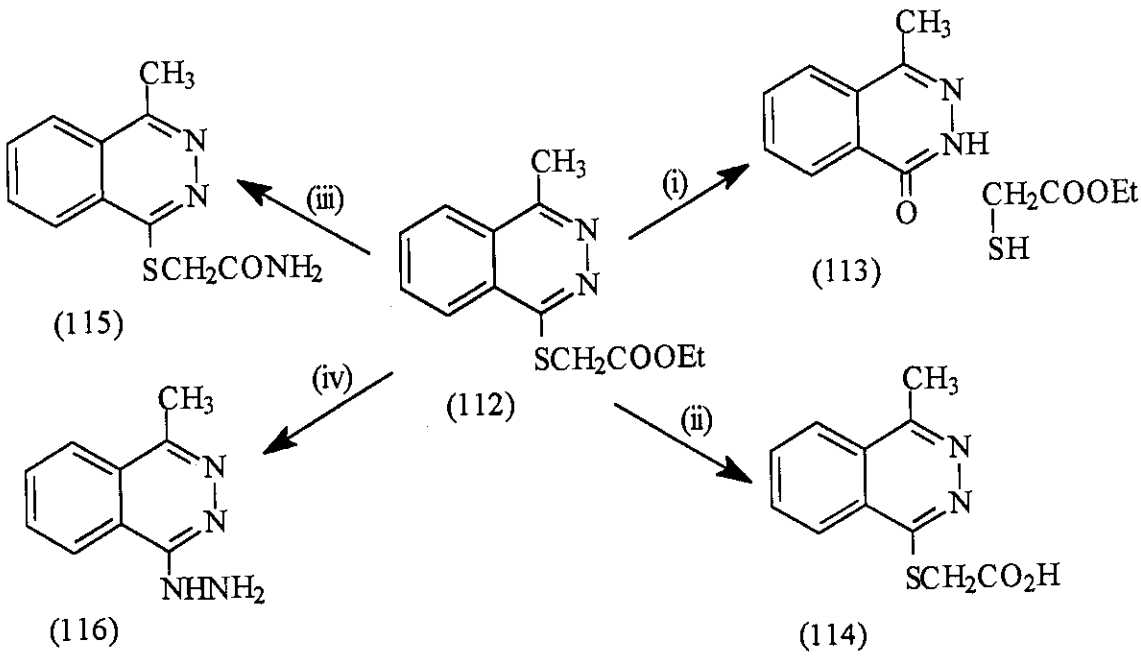
(111)

Treatment of 4-methyl-1(2H) phthalazinthione with ethylbromoacetate in presence of sodium ethoxide gave 1-(ethoxycarbonylmethylthio)-4-methyl phthalazine (112)[50].



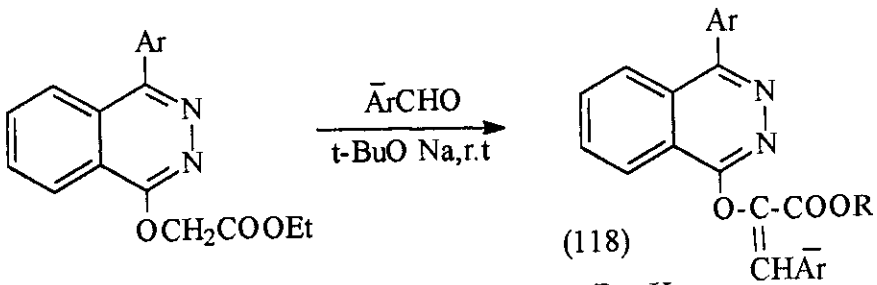
(112)

Hydrolysis of (112) took place under different conditions affording different products. Thus hydrolysis with dil. HCl gave 4-methyl-1(2H) phthalazinone (113), heating with aquous ammonia followed by acidification afforded the acid (114), while treatment of (112) in absolute EtOH with excess ammonia at 0°C gave 1-(carboxyamidomethylthio)-4-methylphthalazine (115).Treatment of (112) with excess hydrazine hydrate in absolute EtOH produced 1-hydrazino-4-methyl phthalazine (116).



(i) dil HCl (ii) NH_3 / Δ H^+
(iii) NH_3 /EtOH 0°C (iv) $N_2H_4.H_2O$

Treatment of ester derivatives (117) with aromatic aldehydes namely, benzaldhyde, *p*-anisaldhyde, *p*-chlorobenzaldhyde and *p*-nitro benzaldhyde in presence of sod. Tert. butoxide (under Stobbe condensation conditions)[14,84], gave cinnamic acid derivatives (118a) in 50-65% yield (major product) and Claisen products (118b) in 30-35% yield (minor yield)[14].

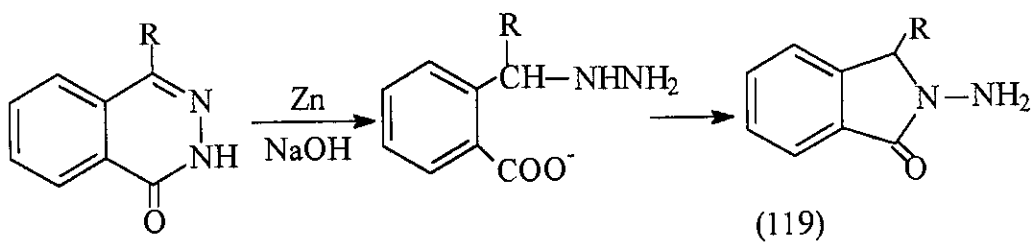


(117)

(118)

(3) Reduction of phthalazinones

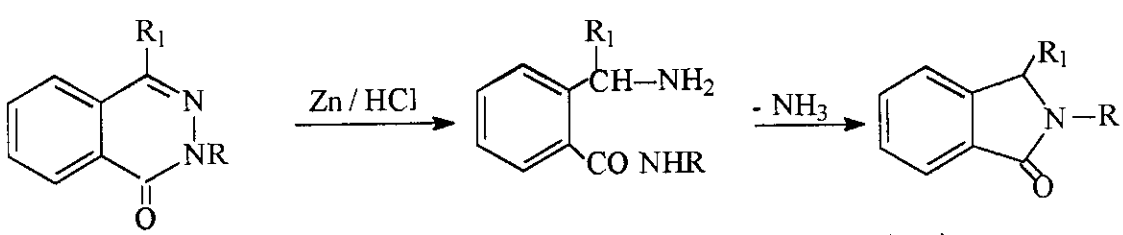
Reduction of phthalazinones afforded different products depending on the reducing agent. Thus, reduction of phthalazone derivatives with zinc and NaOH gave 2-amino phthalamidine derivatives (119)[85].



R = H, COOH

(119)

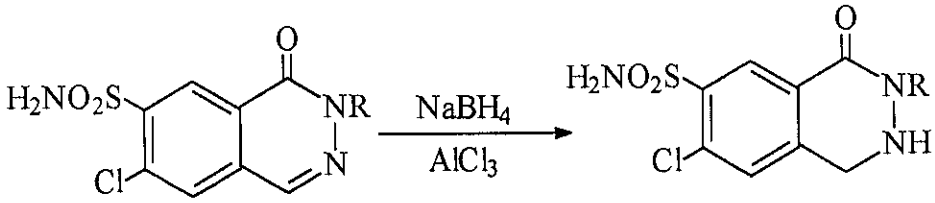
On the other hand, reduction of phthalazones with zinc and HCl involved elimination of the unsubstituted nitrogen as ammonia and ring contraction to phthalimidines (isoindolones) (120)[85-88].



R = H, alkyl, aryl

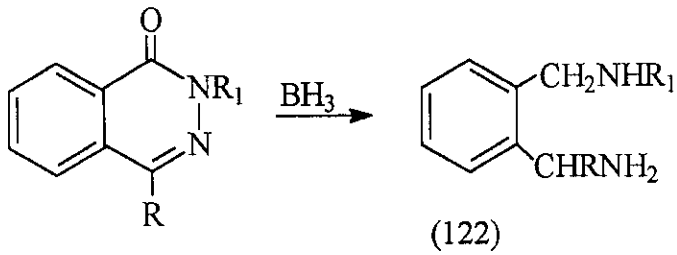
(120)

Specific reduction of the conjugated C=N bond was achieved by using $NaBH_4/AlCl_3$ in diglyme to give tetrahydrophthalazinone (121)[89].



(121)

Reduction of 2,4-disubstituted phthalazine with BH_3 gave α-sub-1,2-benzendimethanamines (122)[90] in high yield.

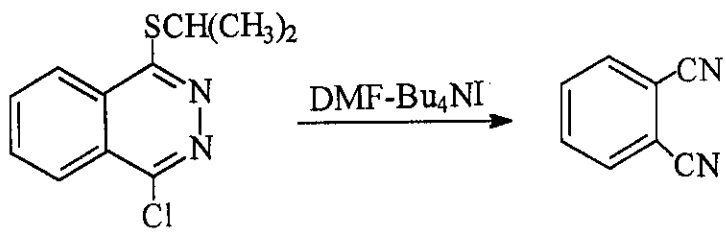


(122)

R = Ph, 4-ClC_6H_4 R_1 = Me, $CHMe_2$

When R=Ph and R_1=H, phthalazinone required sequential treatment with $LiAlH_4$, Pd and H, and finally Raney nickel and H to give resonable yields of (122).

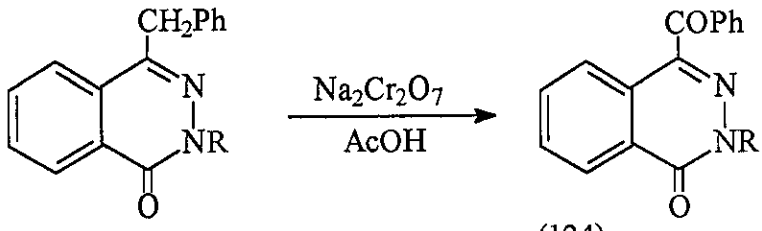
Electrochemical reduction of 1-chloro-4-(isopropylthio)-phthalazine in the DMF-Bu_4NI system resulted in electron transfer and ring cleavage to give phthalo nitrile (123)[91].



(123)

(4) Oxidation of phthalazines:

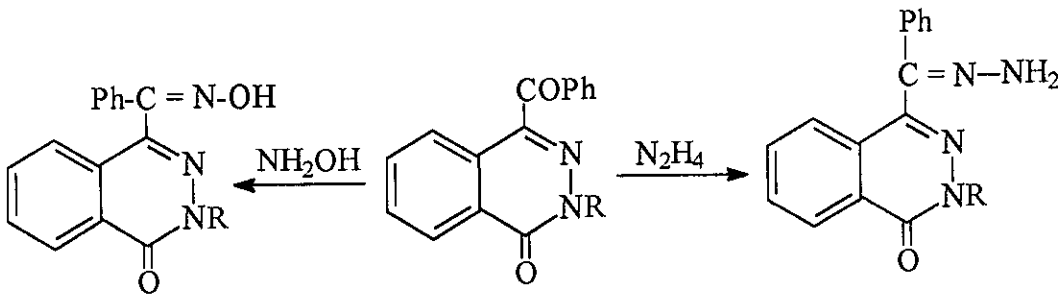
4-Benzyl-2-sub.phthalazin-1-(2H)-one was oxidized by sodium dichromate in AcOH to give the corresponding 4-benzoyl phthalazinone derivatives (124)[92].



(124)

R = CH_3 , $CH_2CH_2CONH_2$, CH_2CH_2CN

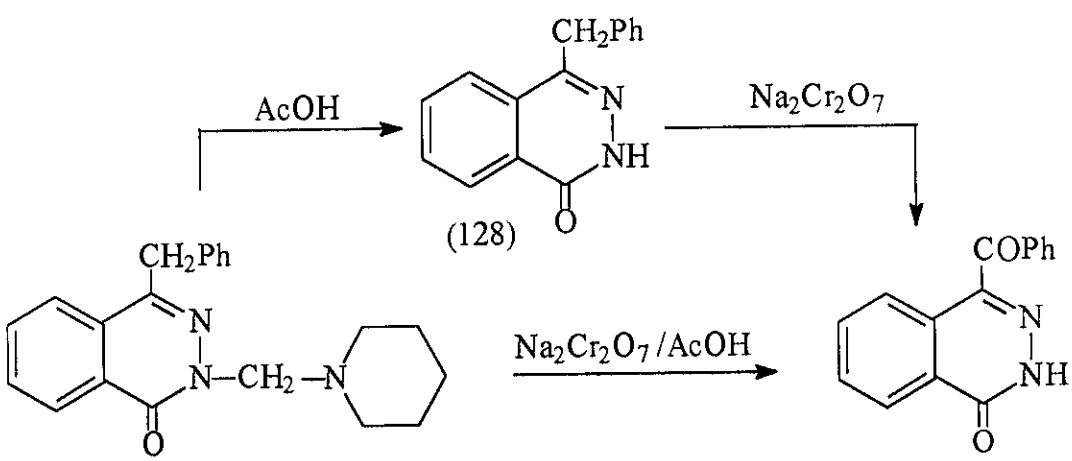
Reaction of (124) with hydroxylamine HCl and hydrazine hydrate afforded the corresponding oxime (125) and hydrazone (126) respectively.



(125) (124) (126)

Oxidation of 4-benzyl-2-piperidinomethyl phthalazin-1(2H)-one (127) (Mannish base) using acetic acid only for short time gave 4-benzylphthalazin-1(2H)one (128) through piperidino methyl cleavage[92].

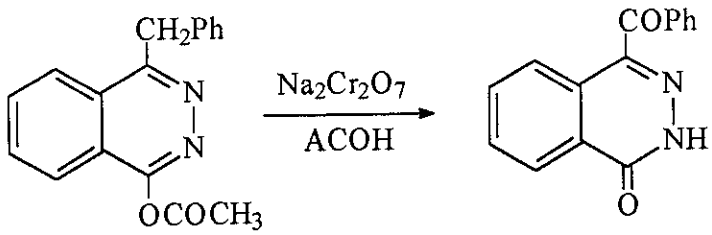
On the other hand carrying out the oxidation for long time using 2 moles of oxidizing agent gave 4-benzoyl phthalazin-1-(2H)- one (129).



(128)

(127) (129)

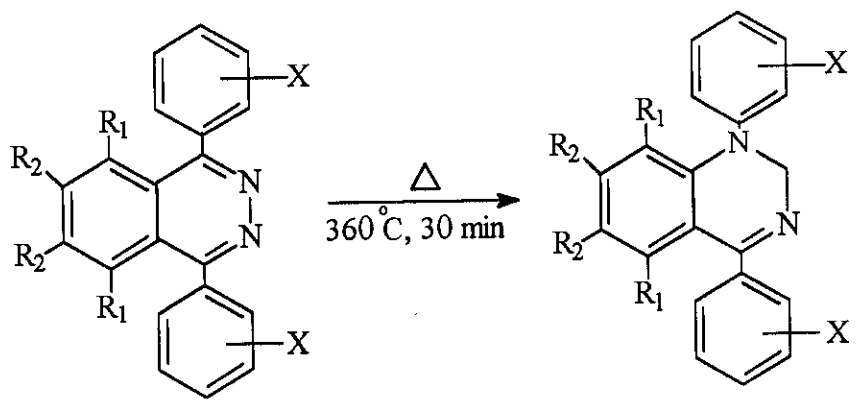
4-benzoyl phthalazinone (129) was also obtained by oxidation of 1-0-acetyl-4-benzyl phthalazine (130) using $Na_2Cr_2O_7$ (AcOH) via ester linkage cleavage.



(130)

(5) Thermal rearrangement of phthalazine:

Heating of polyphenylated phthalazine (131_{b-d}) in sealed tube at 360°C for 30 min gave the corresponding quinazoline (132_{b-d}) in high yield 70% while less stearically crowded phthalazine (131_a) gave low yield of (132_a)[93].



(131)

a) $R_1 = R_2 = H$, X =F

b) R_1 = Ph, R_2 = H, X = H

(132)

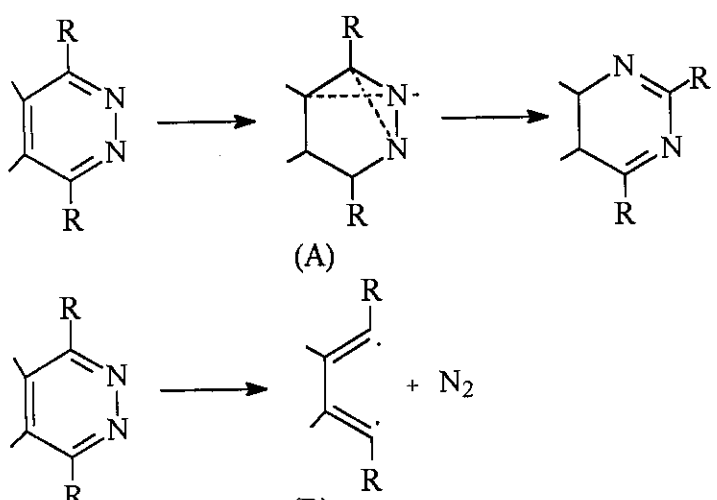
c) R_1 = Ph, R_2 = H , X = H

d) $R_1 = R_2$ = Ph , X = F

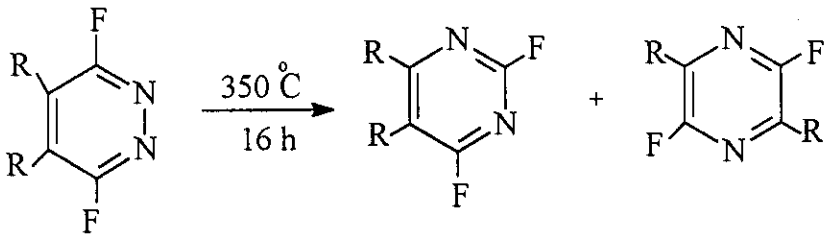
Mechanism of the above rearrangement involved two possible reaction pathways.

(i) Via (benzvalene) type intermediate A

(ii) Via nitrogen elimination under diradical intermediate B.



Thermal rearrangement of phthalazine to quinazoline exhibits some similarity with the case of perfluropyridazine reported by Chambers et al to pyrimidine and pyrazine[94].

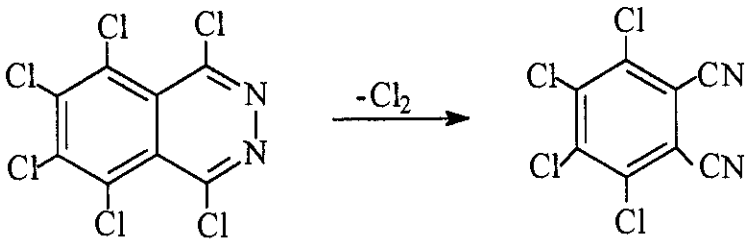


R = $CF(CF_3)_2$

Competition between rearrangement and elimination of nitrogen depends on a number of factors. Thus in pyridazine the fluorine adjacent to the nitrogen destablize radical intermediate, consequently rearrangement reaction is favored over nitrogen elimination[95].

In phthalazine, stearic crowding effect could decrease activation energy required for the rearrangement reaction, hence favoring rearrangement over nitrogen elimination.

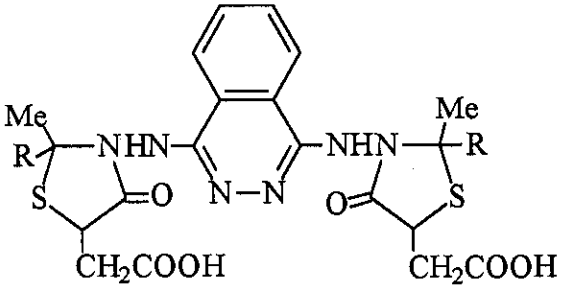
It has also been reported that pyrolysis of hexachlorophthalazine gave the dicyano compounds [96].



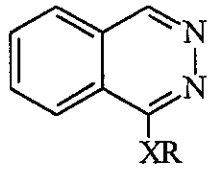
Biological activity of phthalazines

Phthalazine nucleus has been employed as a basis for the synthesis of chemotherapeutic agents and a large number of its derivatives have been reported to possess various biological properties such as fungicides, and antimicrobial.

A large number of phthalazine derivatives (133, 134) have been prepared and tested for their antibiotic activities[97], antipyretics and antiinflammatory action[98-100].



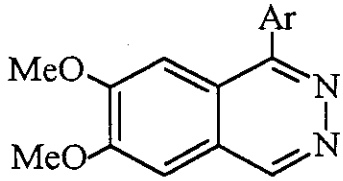
(133)



(134)

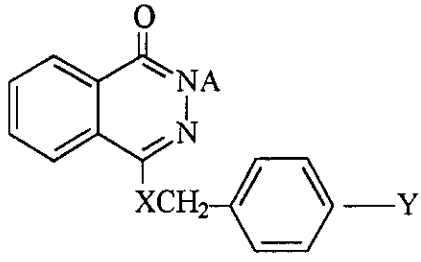
X = 0, S R = sub. alkyl, Ph, Pyridyl

4-aryl-6,7-dimethoxyphthalazines (135) exhibited good anticonvulsant activity [101-102] to prevent audiogenic seizures in mice.



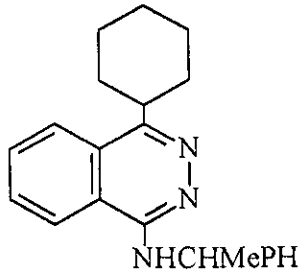
(135)

It was reported that[103] phthalazinone derivatives 136 (A = Ph, pyridyl , x = 0,S, or NH, Y = H, haloalkyl) were prepared as agrochemical fungicides for crops with no toxicity to animals or fish.



(136)

Also, phthalazine derivatives (137) was prepared for treatment and prevention of ischemic tissue diseases caused by blood platelet aggregation [104].

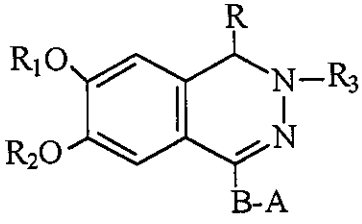


(137)

On the other hand, antimicrobial and antifungal activity of some new 1-methyl phthalazinium compounds were reported [105].

A number of phthalazine derivatives exhibited antihypertensive activity of mild potency and reasonable safety[106-109].

Phthalazine derivatives (138) (B = NH, CH_2, A = un (sub.) phenyl, R = H, aryl, R_1 = alkyl, aryl, R_2 = alkyl) were used as phosphodiasterase-4-inhibitor which are useful for treating allergic and inflammatory pathologies and respiratory diseases [110-111].



(138)

Finally phthalazine derivatives displayed slight antimalarial activity against avian malaria [112].