CHAPTER – I

INTRODUCTION, REVIEW OF LITERATURE AND SCOPE OF THE PRESENT WORK

INTRODUCTION

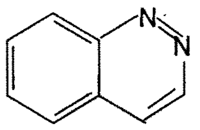
The heterocycles play an important part in the metabolism of all living cells and find important applications in industry.[1] Among these important substances, such vitamins and coenzymes precursors as thiamine, riboflavin, nicotinic acid, adenine, biotin, vitamin B_{12}, vitamin E, photosynthesizing pigment chlorophyll, the oxygen-transporting pigment haemoglobin, the purine and pyrimidine which are the components of the nucleic acids, and their metabolic products such as uric acid, allantoin, and alloxan to the amino-acids like histidine, tryptophan, proline, and the harmones such as kinetin, zeatin, heteroauxin and histamine contain heterocyclic ring system in them.

Many of the drugs, natural as well as synthetic, which are in regular use are heterocyclic compounds. The several natural drugs such as alkaloids, the cardiac glycosides and antibiotics such as penicillin contain heterocyclic ring in them. Some other synthetic heterocyclic compounds are numerous and include barbiturates, thiouracil, carbimazole, 9-aminoacridine, 8-hydroxyquinoline, and vasoprassor modifiers. Polyvinylpyrrolidone are used as a replacement for serum lost in haemorrhage and shock.

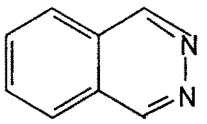
Many pesticides and weed killers such as paraquat, diquat and simazine; insecticides such as rotenone, diazinon, menazon; anthelminitics such as phenothiazine, thiabendazoles; rodenticides such as warfarin are heterocyclic compounds. The heterocycles are acting as the antidotes for poisoning due to the phosphorus insecticides, such as pyridine-2-aldoxime methiodide. The current use of the heterocycles in drugs and pesticides is due to the high resistance of heterocyclic substances to biological degradation. In addition to the drug value the synthetic heterocyclic compounds acts as chemotherapeutic agents, dyestuffs and co-polymers.

The phthalazine and it's derivatives is very interesting class of heterocyclic compounds having wide range of applications in medicinal and synthetic chemistry.

Phthalazine is benzo [d] pyridazine[2] in which the pyridazine ring is fused with a benzene ring in two ways, giving cinnoline or phthalazine.[3]

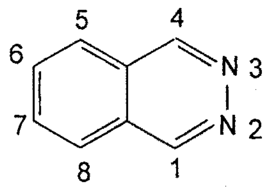


(I) Cinnoline



(II) phthalazine

The numbering system used in chemical abstracts is shown in formula III.[4] However, the phthalazine and it's derivatives, perticularly phthalhydrazides have been numbered as per scheme given below. The chemistry of the phthalazines has been reviewed by Vaughan.[5]



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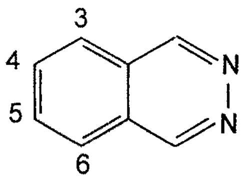
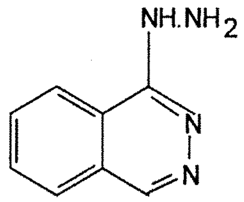


(IV)

Phthalazines are grouped into different classes, viz. Phthalazine, phthalazones, pseudophthalazones and phthalhydrazides.

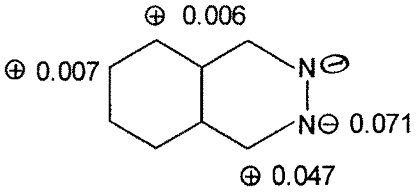
PHTHALAZINE

Phthalazine is a colourless solid with a faint quinoline like odour, and is very less soluble in water and in common organic solvents.[6] The occurance of it in nature has not been recorded. However, hydrallazine (1-hydrazino-phthalazine) is much used to lower high blood pressure in man.[7]



(V) Hydrallazine

The electron density distribution in phthalazine nuclei has been shown below (VI).[8]

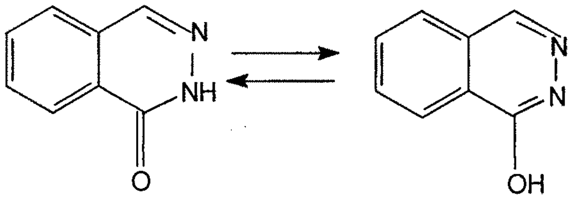


(VI)

PHTHALAZONES

The phthalazones (VII) are tautomeric with 1-hydroxy-phthalazines (VIII)[9], phthalazones carrying a substituent in the

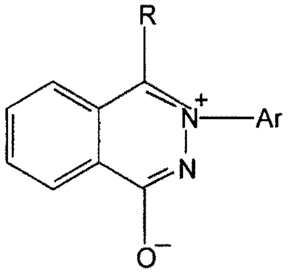
2-position differ considerably in the mode of synthesis and properties from phthalazones carrying a substituent in the 3-position.



(VII) (VIII)

PSEUDOPHTHALAZONES

They are known as 3-arylphthalazinium compounds. 3-Arylphthalazones are apperently exist as the internal phthalazinium salts (IX).[10]

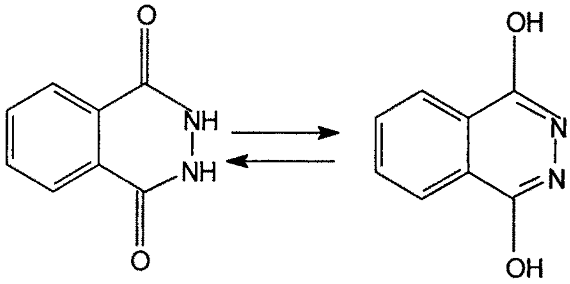


(IX)

Vaughan has suggested the term pseudopthalazone as a generic name for these compounds, and for convenience this terminology is retained. However, in the chemical abstracts the compounds are listed as phthalazinium derivatives.

PHTHALHYDRAZIDES

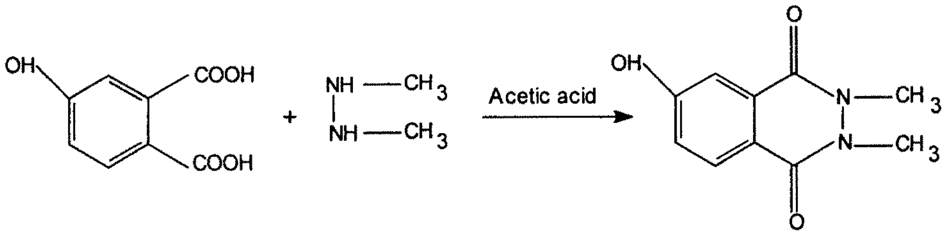
The phthalhyadrazides are 1,4-diketo derivatives of tetrahydrophthalazine. Phthalhydrazide (X) is tautomeric with 1,4-dihydroxyphthalazine (XI). Kanda and Mashima[11] believed that it exists largely in the diol form, confirmed on the basis of Raman spectrum. Phthalhydrazide (X) itself is a white crystalline substance which sublimes at 200^0 and melts at 334^0. Although devoid of basic properties, it is soluble as a non basic acid in sodium hydroxide solution from which it is precipitated by carbon dioxide.



(X) (XI)

LITERATURE SURVEY

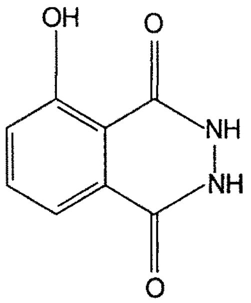
Baeyer[12] prepared 4-hydroxy- N,N '-dimethylphthalhydrazide from 4-hydroxyphthalic acid and syn-dimethyl hydrazine in acetic acid.



(I)

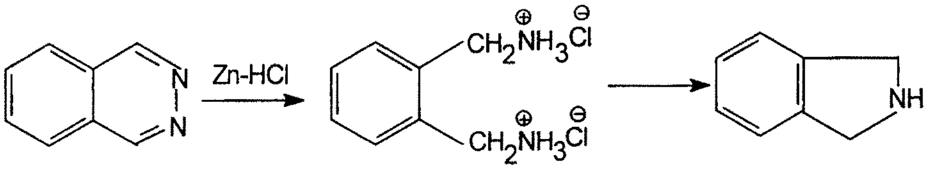
3-Benzamidophthalhydrazide was prepared from the corresponding ester and hydrazine hydrate and then acetylated directly to give diacetyl derivative.[13]

Bernthsen and Semper[14] prepared 3-hydroxypthalhydrazide from 3-hydroxyphthalic anhydride and 3-chlorophthalic acid respectively.



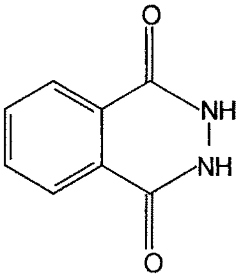
(2)

Phthalazine on vigorous reduction with zinc and hydrochloric acid results in ring cleavage and the formation of the dihydrochloride of α, α ' – diamino-o-xylene.[15] The latter on pyrolysis gives dihydro-isoindole.



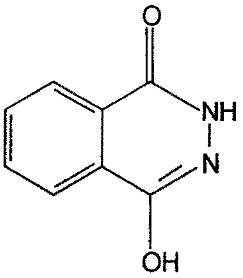
(3)

Forsterling[16] obtained a substance m < 300^0 by the action of hydrazine hydrate on $C_6H_4(CO)_2O$ in ethanol and assigned the formula as shown below :



(4)

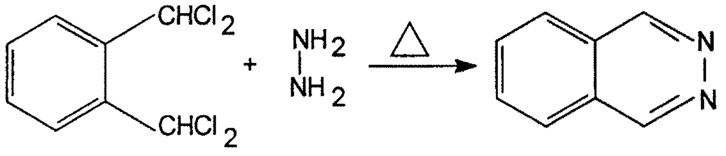
The correct constitution of phthalazine derivative was established by Forsterling.[17]



(5)

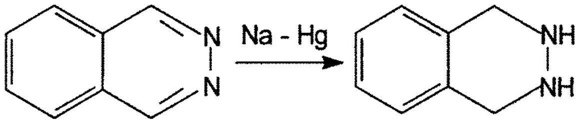
1-hydroxy 4-keto-3, 4-dihydrophthalazine

Gabriel and Muller[18] carried out the condensation of α, α, α ', α '-tetrahalo-o-xylene derivatives with hydrazine which gives phthalazines.



(6)

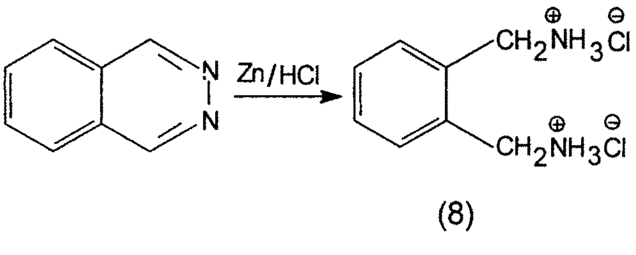
Reduction of phthalazine in presence of sodium amalgam was carried out by Gabriel and Eschenbach[19] to yield tetrahydrophthalazine.



(7)

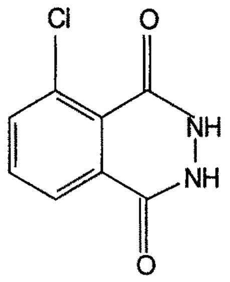
Paul[20] also reduced phthalazine to tetrahydrophthalazine.

Frankel[21] carried out vigorous reduction of phthalazine with zinc and hydrochloric acid which leads to ring opening



(8)

3-Chlorophthalhydrazide was prepared from 3-chlorophthalic acid by Borgert and Boroschek.[22]



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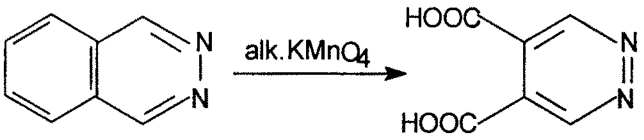
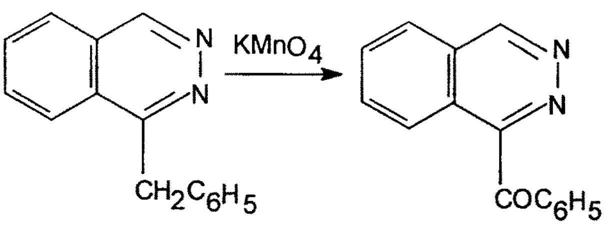
Gabriel showed that the pyridazine ring in phthalazine is more stable than benzene ring. It is not surprising that oxidizing agents attack the benzene ring with the formation of pyridazine-4,5-dicarboxylic acid.



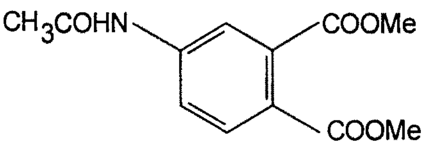
(10)

If, paralleling the quinoline series, an easily oxidizable group present in 1 position of the phthalazine nucleus, may be the point of oxidative attack under mild conditions.[23]



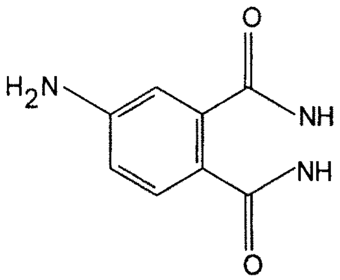
(11)

Borgert and Renshaw[24] prepared 4-acetamidophthalhydrazide from dimethyl-4-acetamidophthalate and hydrazine hydrate.



(12)

4-Aminophthalhydrazide and it's diacetyl derivative m. p. 214^0 were prepared according to Curtius and Hoesch.[25]

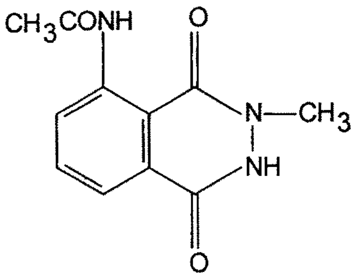


(13)

When an o-diaroylbenzene is condensed with hydrazine, a 1,4-diarylphthalazine results directly.[26]

Schroester and Eisleben[27] obtained o-methylaminobenzhydrazide from the methyl-N-methylanthranilate and hydrazine hydrate in alcohol at 150^0 for eighteen hours.

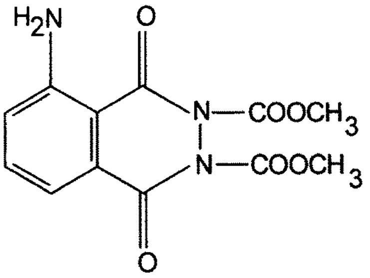
Lawrence[28] obtained α-3-acetamido N-methylphthalhydrazide by the reaction of 3-and 4-acetamidophthalic anhydride with methylhydrazine.



(14)

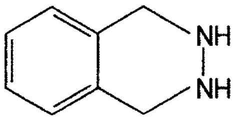
Dan Redulescu[29] carried out the reaction between $N_2H_4 \cdot H_2O$ and phthalimide to give phthalhydrazide, later he carried out experiment at 0^0 but he was unable to isolate the least trace of $C_6H_4(CO)_2N\text{-}NH_2$ and the only intermediate product was unstable ammonium salts of phthalhydrazide.

Albert[30] prepared 3-aminophthalhydrazide and its diacetyl derivative.



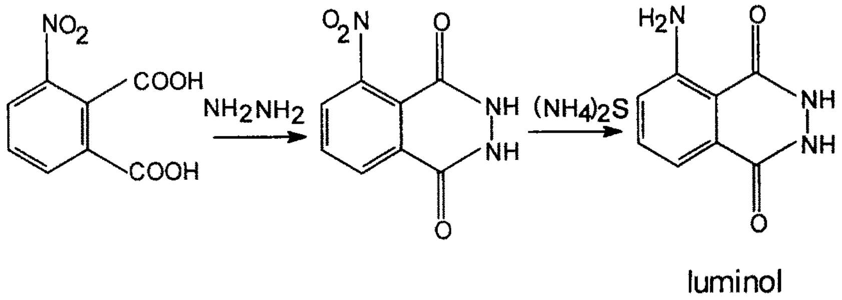
(15)

Seidel and Benzer[31] reduced phthalazine to yield tetrahydrophthalazine in presence of sodium amalgam.



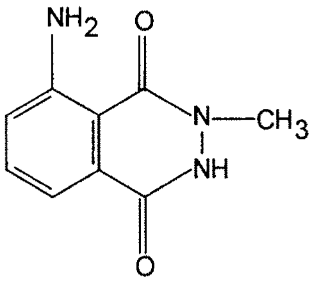
(16)

The preparation of 3-nitrophthalhydrazide from 3-nitrophthalic acid and its reduction to the 3-NH_2 derivatives (luminol) by $(NH_4)_2S$ was carried out by Huntress,Stanley and Parker.[32]



(17)

Zellner and Dougherty[33] prepared 3-amino-N-methyl phthalhydrazide by reducing α -3-N-methylphthalhydrazide with zinc and dilute acetic acid; and acetylating the 3-amino-N-methylphthalhydrazide so obtained.



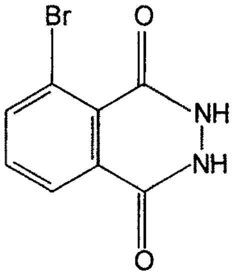
(18)

The brilliant chemiluminescence of 3-aminophthalhydrazide was first investigated by Albrecht, who found that various oxidizing agents, such as ferricyanide and hypochlorite in alkaline solution, were effective in bringing about light emission. The relative chemiluminescence of a number of phthalazine derivatives were measured by means of a photronic cell and galvanometer and effects of structure on the intensity of the light emitted upon oxidation were noted. Measurements were made on the rate of oxidation of derivatives with different groups substituted in the benzene ring and in the hydrazine ring. The effect of hydroxylation and of inhibitors on the rate was noted.[34]

Drew and Garwood[35] studied chemiluminescence of 5-aminophthalazine-1,4-dione and it was shown to be the most powerfully chemiluminescent member of the cyclohydrazide series.

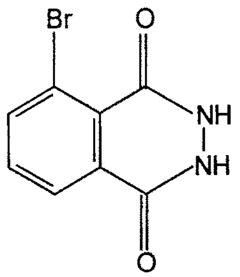
Drew and Garwood[36] reported the isolation of peroxide derivatives of phthalaz-1,4-diones. 5-Aminophthalaz-1,4-dione in 5% of NaOH treated with 30% H_2O_2 and after a time with 96% of EtOH, gives on cooling to 0^0 the Na salt of 5-amino-1,4-dihydroxy-2,3-dihydrophthalazine peroxide $C_8H_8O_4N_3$ Na· H_2O.

Drew and Garwood[37] prepared 5-bromo-1,4-phthalazinedione and studied the chemiluminescence of it. 3-Aminophthalimide, through the diazo reaction gave 3-bromophthalimide which on refluxing with $N_2H_4{\cdot}H_2O$ for 0.5 hour gives the product.



(19)

The preparation of phthalazine derivatives, their chemiluminescence activities, and effect of substituents on chemiluminescence was reported by Drew and Garwood.[38] 5-Bromo and 6-bromophthalazin-1,4-dione were prepared from 3 and 4-bromophthalimide



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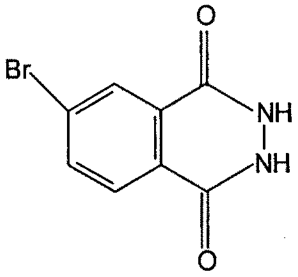


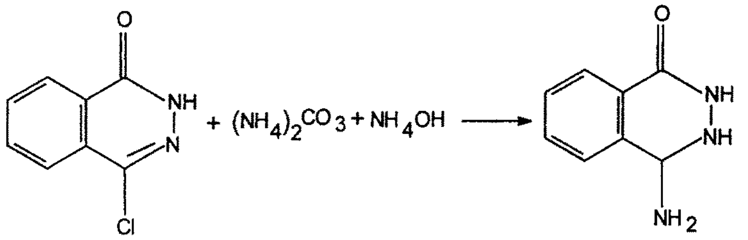
(21)

Erich Schneider[39] reported the chemiluminescence of luminol catalysed by iron complex salts of chlorophyll derivatives.

The luminescent reactions of luminol with a view to blackout illumination was done by A. Steigmann.[40] Photoluminescence and the association of ions in solutions of lead salts of phthalazines were reported by Gorden.[41] The luminescence of luminol III by complex Cu compounds was reported by K. Weber and M. Krajcinovic.[42]

The study of luminescent bacteria was first reported by W. Rytz.[43] Luminescent bacteria on fish produces light only in the presence of oxygen. It was shown that 3-aminophthalic hydrazide in alkaline solution produces light when oxidized by H_2O_2, but only if hemin is present as a catalyst.

Stephenson[44] reported the synthesis of 1-aminophthalaz-4-one from 1-chloro-4-phthalazone, $(NH_4)_2CO_3$ and NH_4OH. The reaction mixture was heated for twenty one hours at 195-210^0 and the residual extracted with boiling water.



(22)

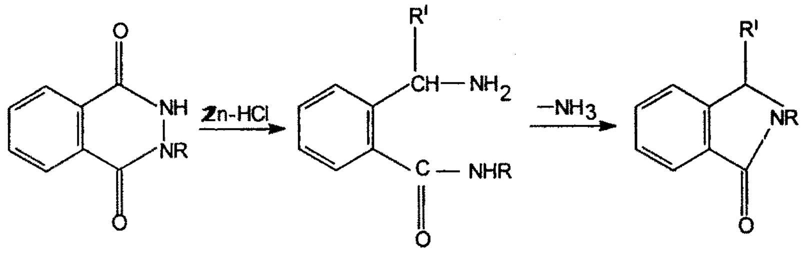
Vaughan and Baired[45] reported the preparation of some phthalazines and related substances. These phthalazines showed some antimalerial activities. The following compounds were prepared.

1) 6-Chlorophthalazone
2) 1,6-Dichlorophthalazine
3) 1-Methoxy-6-chlorophthalazine
4) 7-Chlorophthalazone
5) 1-Methoxy-7-chlorophthalazine
6) 7-Methoxyphthalazone
7) 1,7-Dimethoxyphthalazine

Hydrazine hydrolysis and radical exchange reactions of N-substituted phthalimides in relation to the constitution of the antimalerial was reported by Barber and Wragg.[46]

The preparations of 5 - and 6-diamino-1,4-dioxotetrahydro-phthalazines were reported by Lacey and Brouillard.[47] The reaction proceed smoothly in H_2SO_4 solution. Phthalic anhydride was nitrated with mixed acid to produce 3-and 4-nitrophthalic anhydrides in the usual manner, SO_2 was then bubbled through the solution to free it from HNO_2 and HNO_3. The condensation of above nitro compounds with hydrazine sulfate was carried out in the H_2SO_4 solution. The resulting 3-and 4-nitro-N-aminophthalimides rearrange under the temperature used, 60 – 130^0 in the same solution to form the product which on reduction by sodium hydrosulfide gave the desired products 5-and 6-amino-1, 4-dioxotetra-hydrophthalazines.

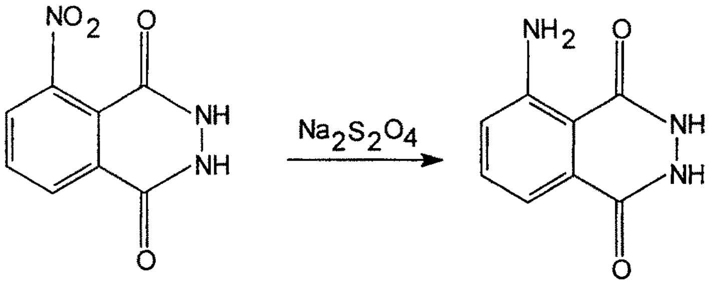
On reduction with zinc and hydrochloric acid, the phthalazones undergo ring contraction of substituents in the 2-, 3- or 4- positions.[48]



(23)

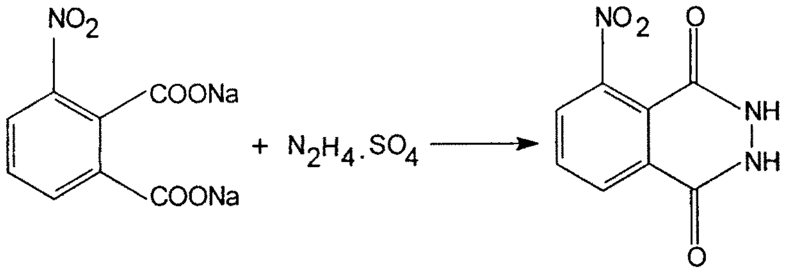
Haworth and Robinson[49] reported the reactions of 1:4-dichloro-phthalazinewith amino, substituted anilino or dialkylamino groups to replace halogen atoms to give amino derivative. These amino derivatives were tested for antimalerial activities. Here, 4-*p*-chloro-anilino-1-β-diethylaminoethylaminophthalazine have shown positive activity against P-gallinaceum. The required dose was 160 mg/kg.

The reduction of 5-nitro-2, 3-dihydro-1, 4-phthalazine-dione with $Na_2S_2O_4$ yield about 80% of the 5-amino compound.[50]



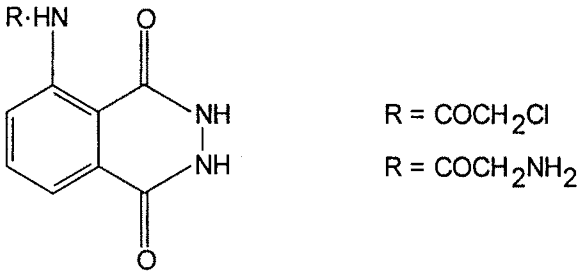
(24)

C. T. Redeman and C. Ernst Redeman[51] reported the synthesis of 5-nitro-2, 3-dihydro-1,4-phthalazinedione from $O_2N{\cdot}C_6H_3(CO_2Na)_2$ with $N_2H_4 \cdot H_2SO_4$.



(25)

Cross and H. D. K. Drew[52] prepared the chemiluminescent compounds. The substitution in the amino group of luminol was done and its effects on the luminescence were studied.



(26)

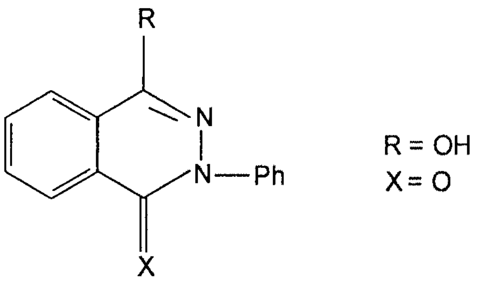
Synthesis of 1 - (3 -amino - 4 - tert-butylphenyl) – 4-hydroxy – phthalazine from O-(3-amino-4-tert-butylbenzyl) benzoic acid and hydrazine was reported.[53]

E.D. Amstutz[54] reported the comparison data of the UV absorption spectra of naphthalene, phthalazine and cinnoline. The solvent used was methylcyclohexane.

3

The preparation of 1:2:5:8:9:10-hexahydro-4-methyl-1-oxophthalazine from condesnation of ethyl 2-acetylcyclohex-4-ene-1-carboxylate with 50% aqueous hydrazine solution and alcohol was reported by Dixon and Wiggins.[55]

A series of compounds derived from 1:2-dihydroxy-4-hydroxy-1-oxo-2-phenyllphthalazine by replacement of one or both oxygen atoms by sulphur has been prepared by Bavin, Drain, Seiler and Seymour.[56] It was tested against mycobacterium tuberculosis. Several related phthalazines were described. These compounds found to exhibit fairly high tuberculostatic activities both *in vitro* and *in vivo*. Because of certain resemblence between the structure of this compound and that of the tuberculostatic thiosemicarbazones, it was of interest to investigate the biological activity of a series of related compounds in which one or both of the oxygen atoms were replaced by sulphur.



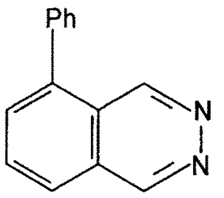
(27)

Atkinson, Brown and Simpson[57] reported some reactions in the phthalazine series. They prepared 1-chlorophthalazine from 1-hydroxyphthalazine and $POCl_3$, 1-phenoxyphthalazine from 1-chlorophthalazine and phenol, 1-aminophthalazine from 1-phenoxyphthalazine and ammonium acetate, 1-chloro-7-nitrophthalazine from 1-hydroxyphthalazine and $POCl_3$, 1-methoxy-7-nitrophthalazine from 1-chloro-7-nitrophthalazine and methanolic sodium methoxide.

Some sulphanilamide derivatives from 1-aminophthalazine were reported by Rodda.[58] 1-*P*-Nitrobenzenesulphonamide phthalazine was prepared from *p*-nitrobenzenesulphenyl chloride and 1-aminophthalazine, in anhydrous pyridine. 1-Sulphanilamidophthalazine was prepared from 1-*p*-nitrobenzenesulphonamidophthalazine reduced in presence of iron.

Re-investigation of the preparation of phthalazine by cyclodehydration of acyl hydrazones was done by Rodda and Rogasch.[59] The preparation of substituted phthalazines by Aggarwal's method involving cyclodehydration of acylhydrazones, has been critically examined. This method does not infact lead to the formation of phthalazines, the products are azines resulting from fragmentation of the starting material.

Atkinson and Sharpe[60] reported the synthesis of some phthalazine derivatives. 1:4-Dihydro-5-phenylphthalazine was prepared from 3-phenylphthalic acid or anhydride. 1:4-Dihydroxy-6-phenylphthalazine was prepared from 4-phenylphthalic acid and hydrazine. It was converted into the 1:4-dichloro derivatives, reduction of this with red phosphorus and hydroiodic acid gave 6-phenylphthalazine.



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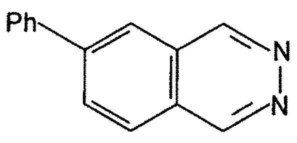
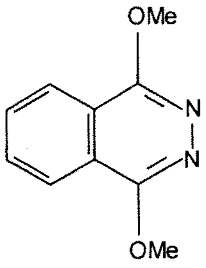


(29)

Some methyl derivatives of phthalhydrazide were prepared by Elvidge and Redman.[61]



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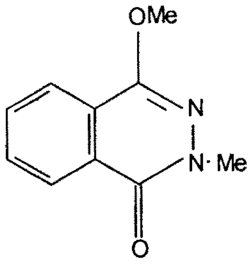

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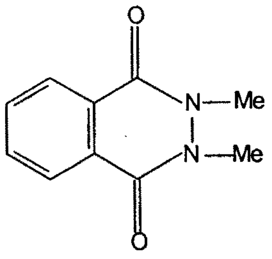

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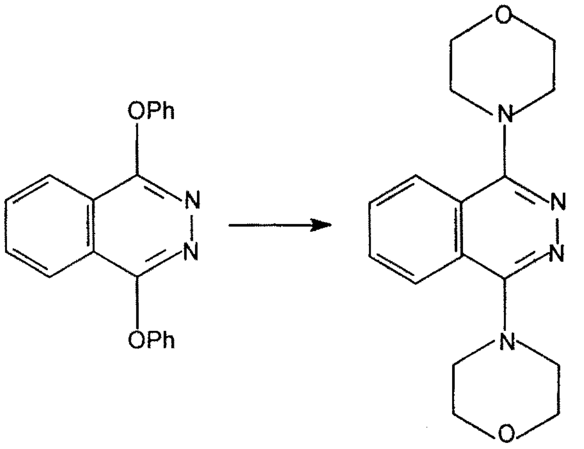
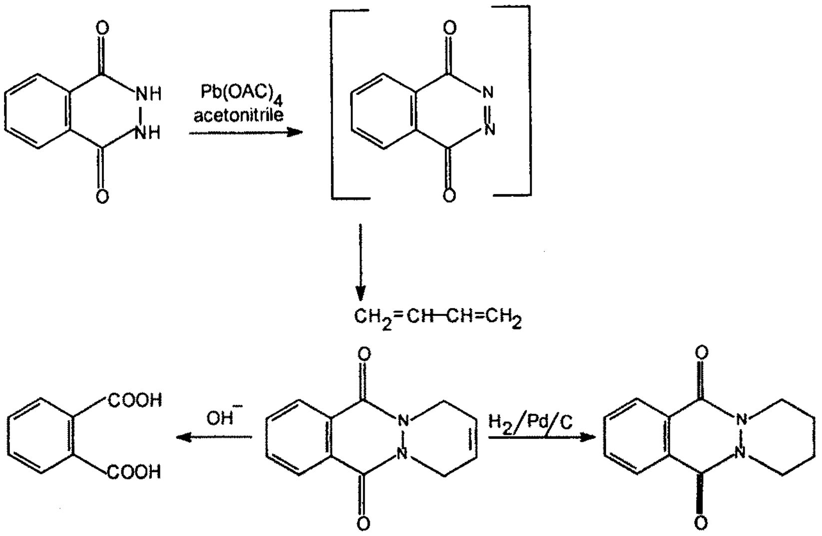


(33)
1,4-diphenoxyphthalazine

(34)
1,4-dimorpholinophthalazine

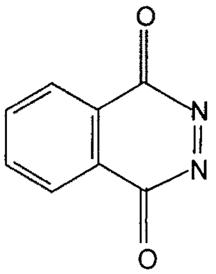
Robert A. Clement[62] studied the oxidation of 2,3-dihydro-phthalazine-1, 4-dione with lead tetraacetate. He reported the following changes.



(35)

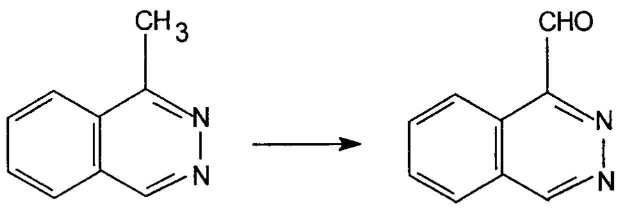
(36)

Preparation of 1,4-phthalazinedione by using oxidation method was reported by Kealy.[63] Here, the low temperature oxidation of the corresponding cyclic hydrazide was done. t-Butyl hypochlorite was found to be perticularly effective for this oxidation since it was soluble in various organic solvents at low temperatures and does not give large amounts of inorganic products. Using this reagent with alkali metal salts of the corresponding hydrazides he prepared 1,4-phthalazinedione.



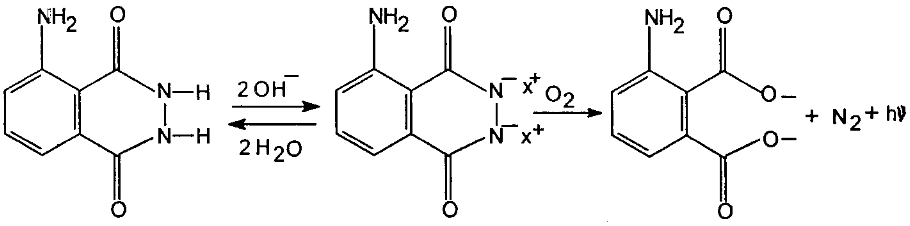
(37)

Synthesis of phthalazine-1-aldehyde was reported by Stephenson.[64]



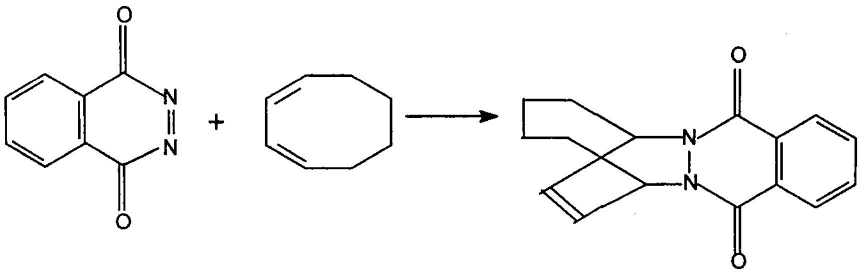
(38)

The chemiluminescence study of luminol and related hydrazides in relatively non acidic solvents, the light emission step has been studied by White and Co-workers.[65]



(39)

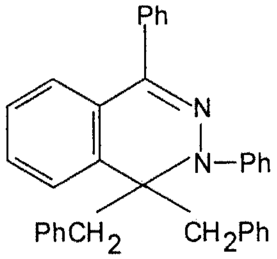
1,2-Cycloaddition of an azo group to an olefin was first reported by Chapmann and Dominianni.[66] This process provides a one step synthesis of a derivative of diazacyclobutane.



(40)

Phthalazine-1,4-dione adduct

Balwant Singh[67] reported the photochemical rearrangement of 1,1-dibenzyl-1, 2-dihydro-2, 4-diphenylphthalazine.



(41)

Cyclization of 1-hydrazino-4-alkyl(aryl)phthalazines with aliphatic acids, orthoesters, cyanogen bromide, urea or carbon disulfide gave the appropriate 3-substituted 6-alkyl(aryl)-5-triazolo [3,4-a] phthalazines in good yield. This was prepared by Potts and Lovelette.[68]

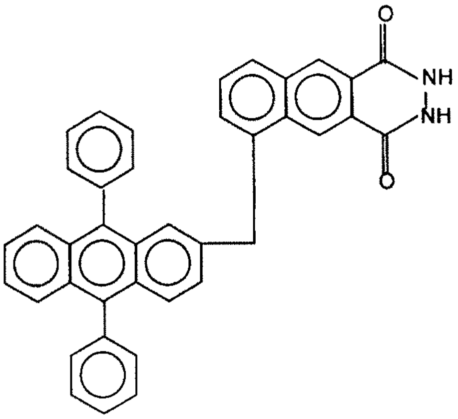
Energy transfer of chemiluminescence was reported by Roswell, Paul and White.[69] They synthesized -

a) 2,3-dihydro-6-[(9,10-diphenyl-2-anthryl)methyl] benzo-[9] phthalazine -1,4-dione. (42)

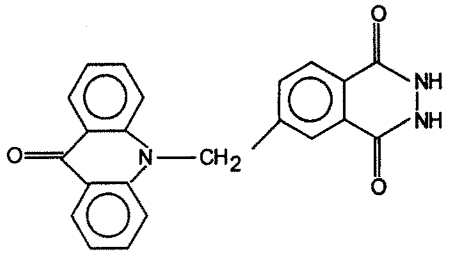
b) 2.3-Dihydro-6-[9-oxo-10-acridanyl)methyl] phthalazine-1,4-dione. (43)

c) 2,3-Dihydro-6-[(9-carbazoyl) methyl]phthalazine 1,4-dione.

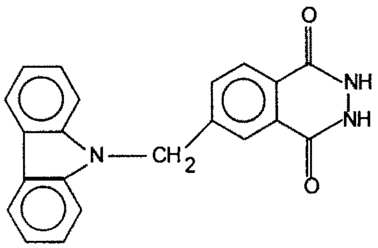
(44)



(a) (42)

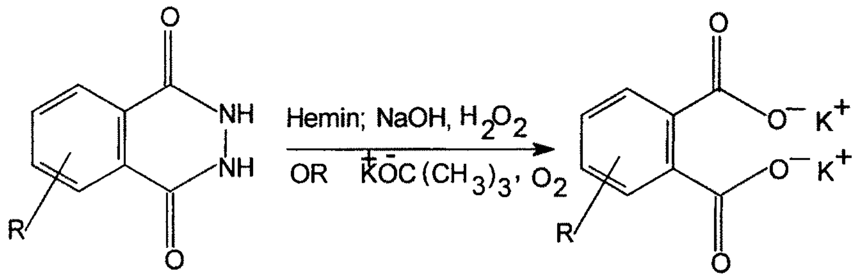


(b) (43)



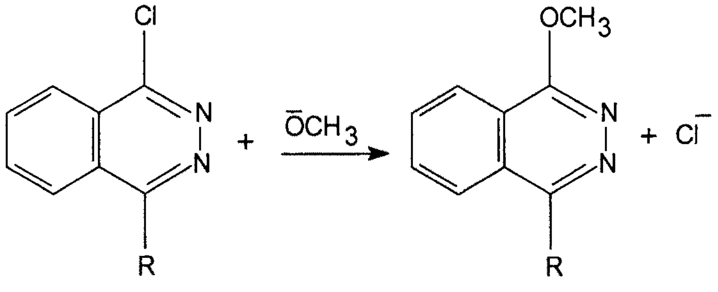
(c) (44)

Roberts and White[70] reported the chemiluminescence study in 2,3-dihydrophthalazine-1,4-dione.



(45)

Hill and Ehrlich[71] investigated the kinetics of the methoxydechlorination of series of 1-chloro 4-substituted phthalazines and related compounds.



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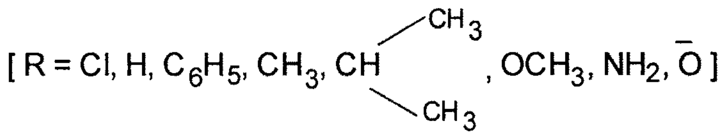
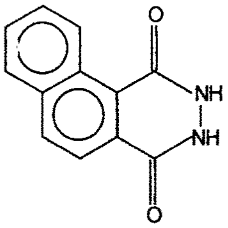


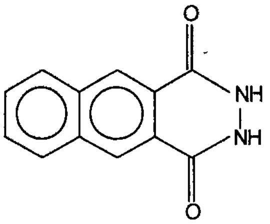
$$[\,R = Cl, H, C_6H_5, CH_3, CH(CH_3)_2, OCH_3, NH_2, \bar{O}\,]$$

The synthesis and chemiluminescence quantum yield of following compounds were reported by Brundrett and Co-workers.[72]



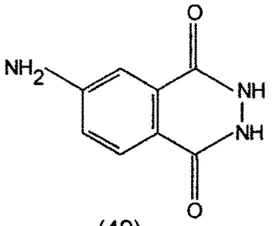
(47)

Benzo [F] 2,3-dihydrophthalazine-1,4-dione



(48)

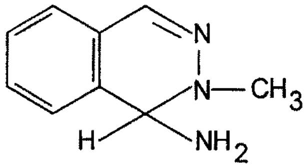
Benzo [g]-2,3-dihydrophthaladizine-1,4,dione



(49)

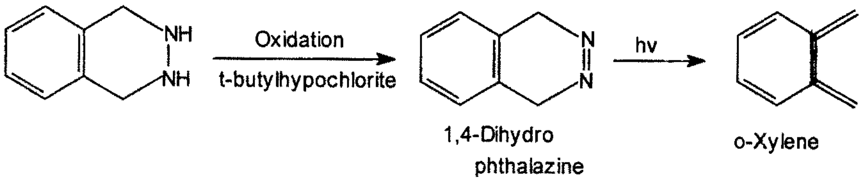
6-Amino-2,3-dihydro-1,4-phthalazinedione

Covalent amination of heteroaromatic compounds were reported by Zoltewicz and Co-wokers.[73] The discovery that the heteroaromatic molecules may be transformed into their covalent hydrates in aqueous solution is of great importance. In the hydration process a water molecule or hydroxide ion serving as a nucleophile adds to a ring carbon atom to give a hydroxy derivative. This brings about major change in physical and chemical properties of the original substance. They carried out structural transformations involving heteroaromatic molecules in ammonia solvent to phthalazine.

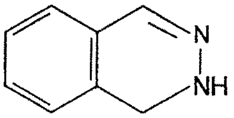


(50)

Photochemical preparation of o-xylene from 1,4-dihydro-phthalazine reported by Flynn and Michl.[74] They also reported the electronic spectroscopy study results and calculations of some phthalazines.

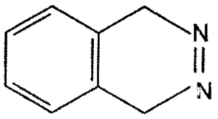


(51)



1,2-Dihydrophthalazine

(52)

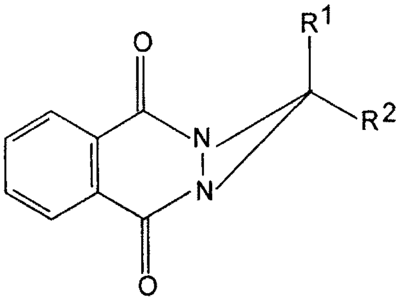


1,4-Dihydrophthalazine

(53)

Uv : 310 - 330 nm 360 nm

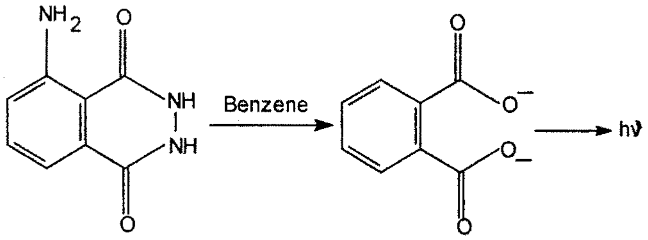
Heine and coworkers[75] reported the isomerization of 1,1-dialkyl-1,4-diazirino[1,2-b]phthalazine-3,8-diones in boiling toluene into 2-[1-alkene-l-yl]-4-hydroxy-1(2H)-phthalazinone and react with enamines to yield derivative of pyrazolo [1,2-b] and indazolo [1,2-b] phthalazinediones.



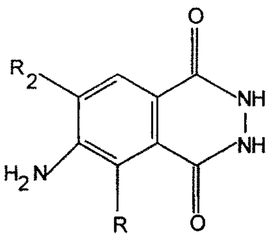
(54)

1,1-Dialkyl -1,4-diazine [1,2-b] phthalazine-3,8-diones]

Alkyl derivative of luminol (5-amino 2,3-dihydrophthalazine-1,4-dione) and some alkyl derivatives of isoluminol (6-amino-2,3-dihydrophthalazine-1,4-dione) were prepared and their chemiluminescence quantum yields were reported by Brundrett and White.[76]

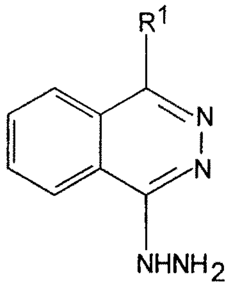


(55)

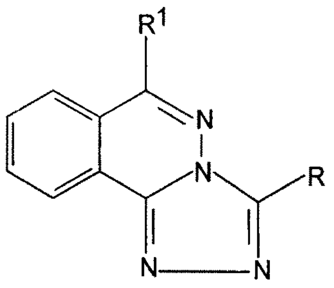


(56)

The acylation of 1-hydrazinophthalazine (1,hydrallazine) with mono, di, tri and tetra-carboxylic acids and acid derivatives gave 3-substituted 5-triazolo [3,4-a] phthalazines. Use of *p*-nitrophenol ester of carboxylic acids facilitates the dehydrative cyclization reaction and enlarges the scope of this type of reaction considerably. Though the annelation of five membered rings to the phthalazine ring proceeds with exceptional case, fusion of six membered ring to this system proceeds with difficulties only. Annelation with larger rings met with failure.[77]

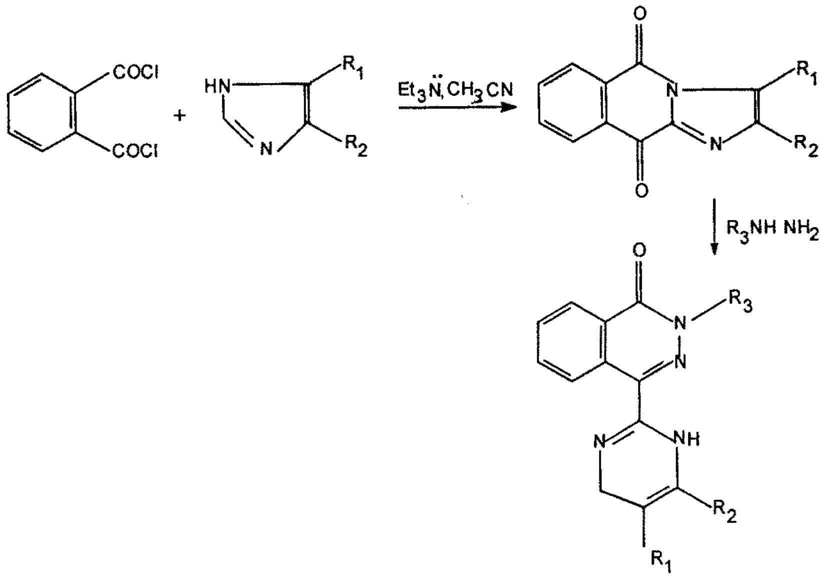


(57)



(58)

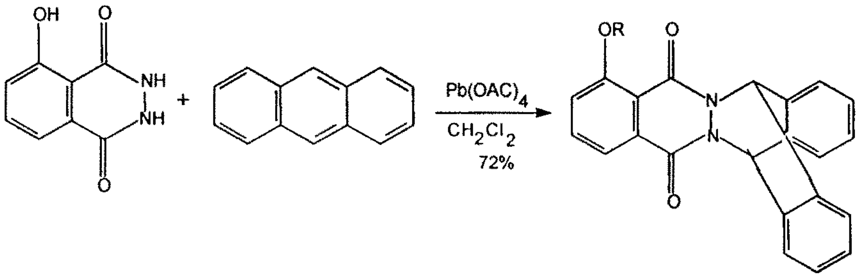
A convinient two step synthesis of 4-(2-imidazolyl)phthalazones from o-phthaloyl dichloride was reported by A. L. Johnson.[78] The imidazo-[1,2-b]isoquinolines-5,10-diones derived from the condensation of equimolar amount of o-phthaloyl dichloride and an imidazol in the presence of 2 molar equivalent of Et_3 N react readily with hydrazines R_3NH NH_2 (R_3= H, alkyl, aryl) to form 4-(2-imidazolyl) phthalazones (59).



(59)

Phenyl and α-cumyl substituted tetrahydrophthalazinediones affords the corresponding hydrazyl radicals. These radicals are transient and unisolable, dicomposing within 48 hours. Cyclic diacylhydrazyl radicals form 1,3,4-oxadizolidine-2, 5-diones, pyridazine-3,6-diones, and phthalazine-1, 4-diones.[79]

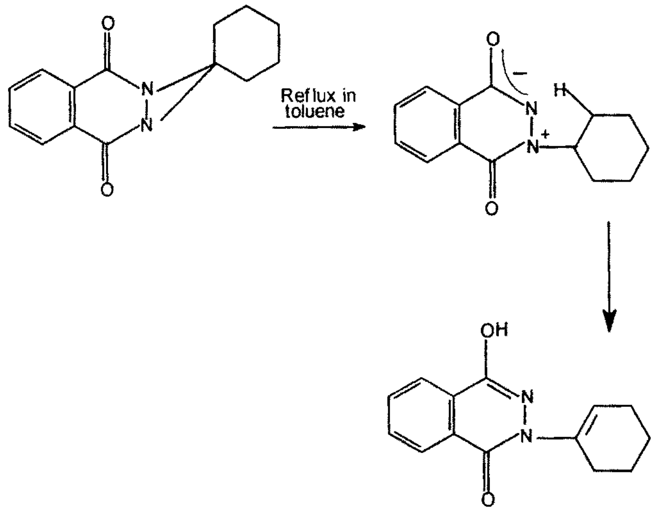
5-Hydroxy-2, 3-dihydro-1, 4-phthalazine-dione was treated with lead tetraacetate in the presence of anthracene to furnish the Diels-Alder adduct. The adduct (R=H) could be protected as its methyl or methoxymethyl ether and then pyrolyzed in the vapour phase at 500^0 to furnish the required 3-alkoxybenzocyclobutane-1,2-dione.[80]



R=H (60)

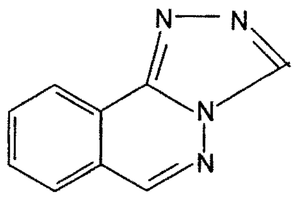
Magnetic circular dichroism of phthalazine was carried out by Vasak, Whipple and Michl.[81]

Novel rearrangement of diaziridine was reported by Heine.[82] 1,1-Dialkyl-1H-diazirino [1,2-b] phthalazine-3,8-diones isomerise in refluxing toluene into 2-(1-alkene-l-yl)-4-hydroxy-1-(2H)phthalazinone.



(61)

Photochemical synthesis of 7,8,9,10-tetrahydro-S-triazolo [3,4-a] phthalazine.[83]



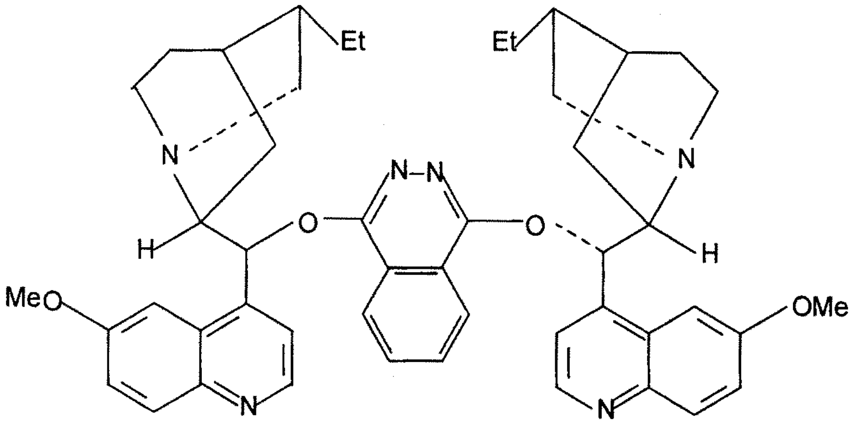
(62)

Hydrogenation and reduction of nitrogen containing heteroaromatics, electron transfer and radical induced dimerization of phthalazine was reported by Corbin and Co-workers.[84] The reaction of Cp_2Ti $(CO)_2$ with phthalazine results in electron transfer upon complexation, leading to the formation of a bimolecular complex bis [bis(h^5-cyclopentadienyl) (phthalazine) titanium] II. They prepared complex in inert atomosphere.

$Cp_2Ti\ (CO)_2$ + Ligand in THF

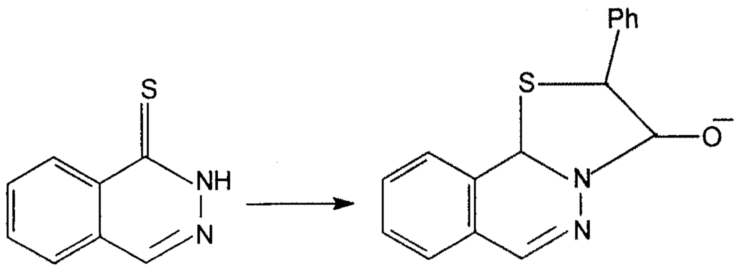
Electron-impact mass spectroscopy, single crystal structure determination, bond distance, bond angle study was done by them.

Evidence for triplet state sublevel selective photochemistry in phthalazines was reported by Leinwand.[85] The rate of oxidation can be a sensitive function of the olefin substitution pattern. The rate of substitution dependent on the nature of the accelerating ligand used. The ligand used is 1,4-bis [9,10-dihydroquinidyl] phthalazine [$(DHQD)_2PHAL^4$] as ligand.



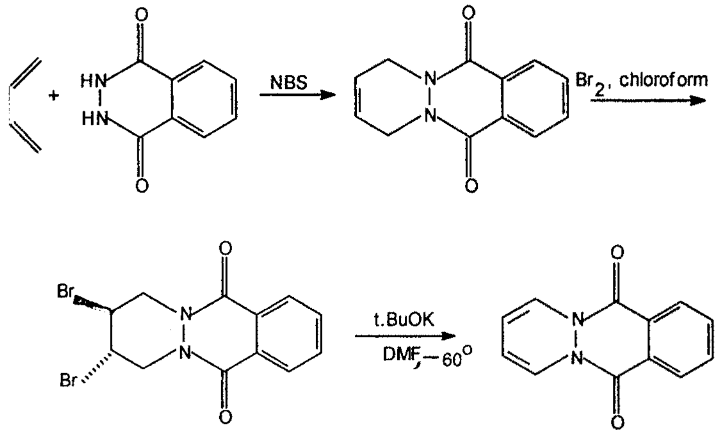
(63)

Annulation to the phthalazine ring system utilizing mesoionic ring was reported by Potts and Salsburg.[86] 1(2H)-Phthalazinethione, readily prepared from 1-(2H)-phthalazinone and P_4S_{10} in dry pyridine, gave with α–bromophenylacetyl chloride in anhydrous ether in the presence of Et_3N (2 mol) anhydro-3-hydroxy-2-phenyl thiazolo [2,3-a] phthalazinium hydroxide 90% (64).



(64)

Sheradsky and Moshenberg[87] reported the preparation and photolysis of 2-phenyl-S-triazolo [1,2-a] pyridazine-1,3-dione and of pyridazino [1,2-b]phthalazine-6, 11-dione.



(65)

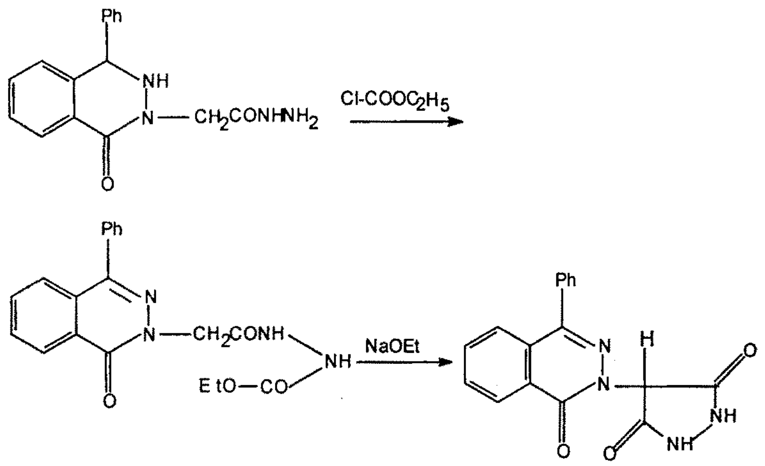
Mandal, Thompson and Hanson[88] reported two examples of hydroxopyridazine and phthalazine ligands which exhibit both antiferromagnetic exchange between the copper centres and sequential two electron reduction at the same positive potential.

Synthesis of antiatherosclerotic agents and phthalazinol derivatives was reported by Yukuo and coworkers.[89]

Dewar and Davidson[90] reported that light obtained from the reaction between dihydrophthalazinedione (DPD; e.g. luminol or isoluminol) as an oxidant and a peroxidase is enhanced by addition of an o-or p-imidazolyl –or benzimidazolylphenol.

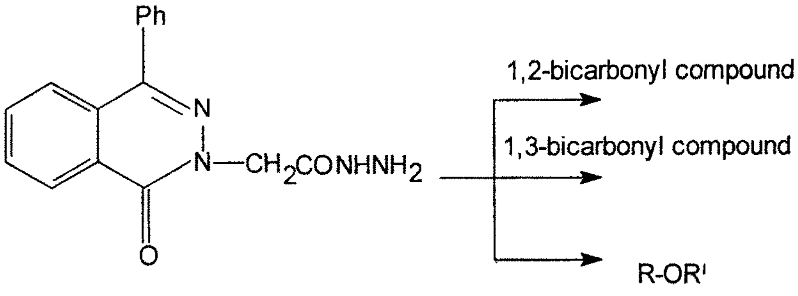
K. Krishnakutty and Thankarajan[91] have reported that phthalahydrazidylacetylacetone can be used as a suitable chemiluminescent indicator in EDTA titration of Mn(II), Ni(II), Zn(II), Cd(II) and Mg(II). Applicability of the indicator in highly coloured solutions has also been demonstrated.

Synthesis and reactions of phthalazine derivatives was reported by Gendy and Abdel-Rahman.[92] The reactions of 1(2H)-oxo-4-phenylphthalazine-2-acetic acid hydrazide with halo compounds such as ethyl chloroformate, monochloroacetic acid, dichloroacetic acid, chloroacetaldehyde, diethylacetal, chloroacetylchloride, phenacyl-bromide, chloroacetamide and acetylene tetrachloride and those of 1(2H)-oxo-4-phenylphthalizine-2-acetic acid N^2-carbethoxyhydrazide with primary amines such as O-phenylenediamine, hydrazine hydrate, thiosemicarbazide, aminoguanidine and guanidinehydrochloride.



(66)

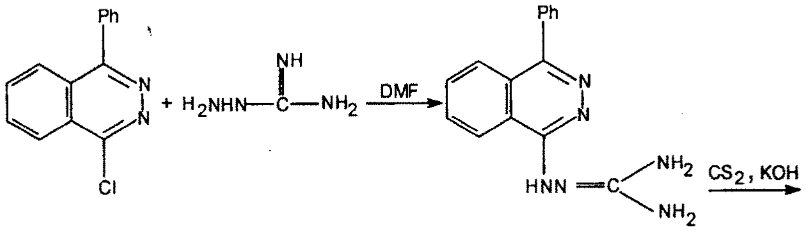
Acylation and condesnsation of 1(2H)-oxo-4-phenylphthalazine - 2-acetic acid hydrazide with esters, acid chlorides,oxoacids, ketones and 1,2-and 1,3-bicarbonyl compounds have been carried out to get heterobicyclic compounds and substituted heterocyclylmethanes.[93]



A number of heterocyclic systems bearing 4-phenylphthalazine-l-yl moiety have been syntehesised by interaction of 1-(4-phenyl-phthalazine-l-yl amino) guinidine and thiosemicarbazide with α,β-bifunctional compounds in neutral or alkaline medium. Some of them have been evaluated for their antifungal activity against *Aspergillus niger* and *Penicillium oxalicum.*[94]

Reaction of 1-chloro-4-phenylphthalazine with amino guanidine bicarbonate and thiosemicarbazide to give heterocyclic systems bearing 4-phenylphthalazinyl moiety especially at positon-1 and evaluate their antifungal activity.

The starting compound 1-(4-phenylphthalazin-l-yl amino) guanidine was prepared by reacting 1-chloro-4-phenylphthalazine with aqueous aminoguanidine bicarbonate in the presence of DMF. Compound (67) underwent cyclisation with CS_2 under reflux in the presence of aqueous KOH to give 3-amino-1-(4-phenylphthalazin-l-yl)-s-triazolo-5-thione (68).



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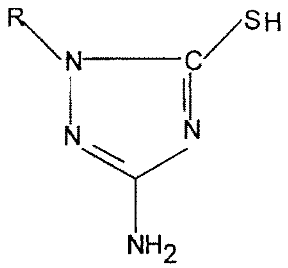
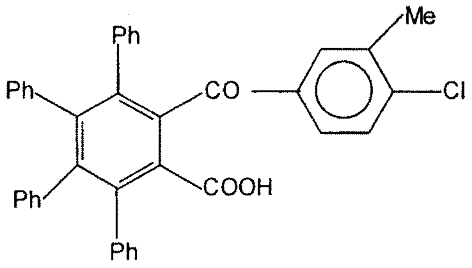
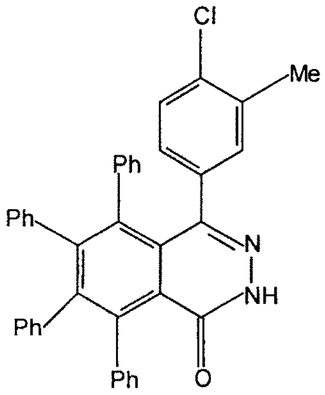


(68)

The interaction of tetraphenylphthalic anhydride with o-chloro-toluene under Friedel Crafts conditions gives 2-(4-chloro-3-methyl) benzyl-3,4,5,6-tetraphenyl benzoic acid (69), which on reaction with hydrazine derivatives gave phthalazinone[95] e.g. (70).

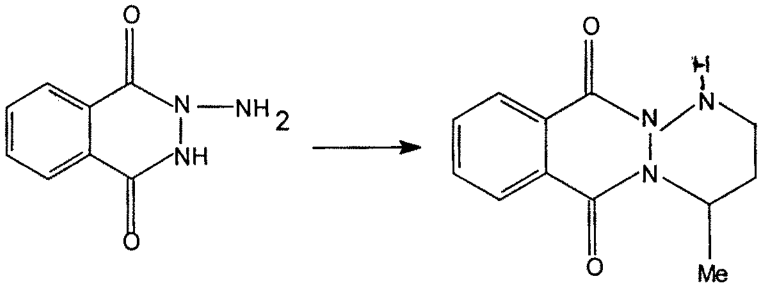


(69)



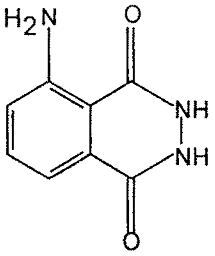
(70)

Synthetic studies on Fused nitrogen heterocycles from N-amino-N,N'-dihydrodiazinediones. Tetrahydrodioxotriazinophthalazine was prepared from aminodihydrophthalazinedione.[96]



(71)

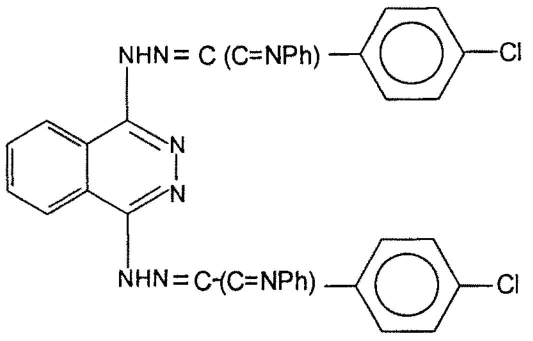
Chemiluminescent determination of nucleic acids or proteins was reported by Keihei, Fumio and Tadanoba.[97] This method for determination of specific nucleic acid or protein in a sample comprises contacting the sample with a chemiluminescent substance e.g. luminol.



(72)

Synthesis of some dihydrallazine derivatives and their multiple pharamacological activities were reported by Joshi and Upadhay.[98] Formazans, 4-thiazolidinones, acetonitriles, and sulfonamids having

1,4-dihydrallazine moiety, e.g. 73) were synthesized. These compounds were screened for their antimicrobial and hypotensive activity.

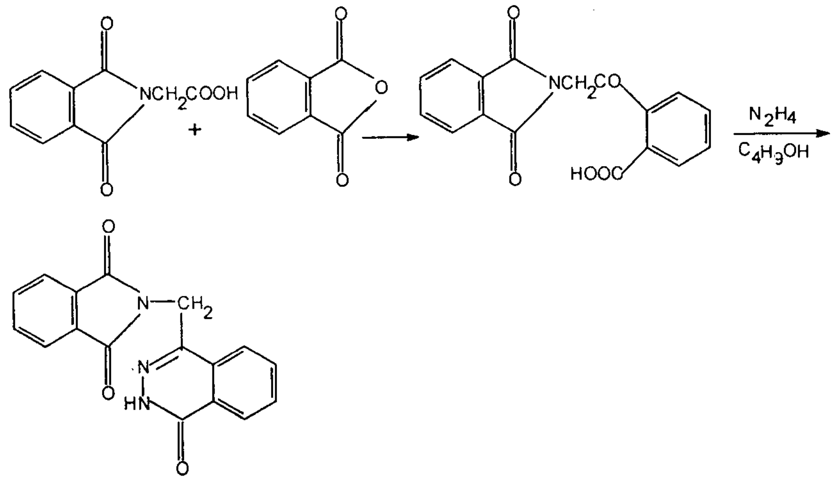


(73)

Speranskij and Co-workers[99] reported the method for determining antioxidant activity of drug. They used phthalazine derivatives e.g. luminol for this purpose.

Douglass[100] reported use of phthalazines in electrogenerated chemiluminescence study. Here, detection based on the reaction of luminol and H_2O_2 has been developed for capillary electrophoresis.

Synthesis and reactions of 4-substituted phthalazines were reported by Mohamed and M. EL-Komy.[101] 4-(Substituted)methyl-1-(2H)-phthalazinones and other phthalazine derivatives have been stynthesized from phthalglycine and phthalanine as starting material.



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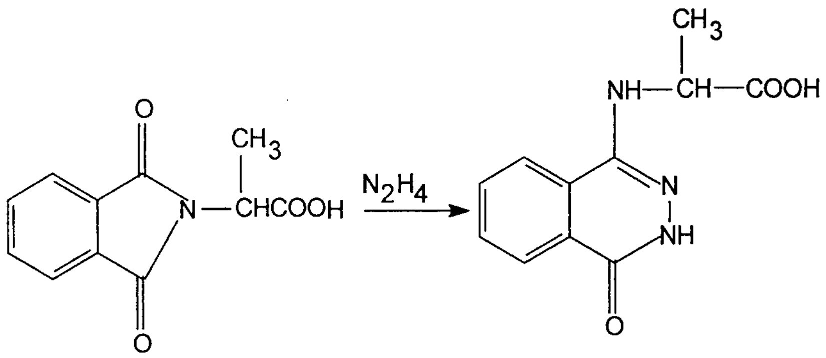
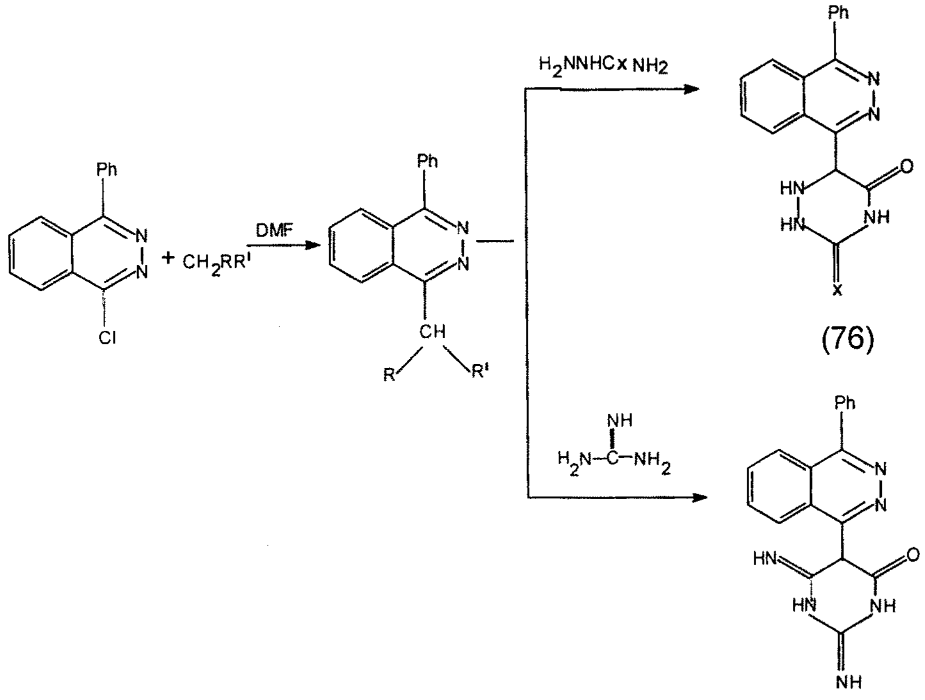


(75)

1-Chloro-4-phenylphthalazine reacts with active methylene compound, and the resultant products undergo cyclocondensation with bifunctional nitrogen compounds leading to the formation of various heteroaryl system.[102]



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(77)

A method was developed for determining total organic carbon (TOC) in water based on the oxidation of organic carbon to CO_2 by $K_2S_2O_8$ at 210^0 in acid medium and CO_2 enhances the chemilumine- scence of a luminol system.[103] (Luminol-H_2O_2-Co^{2+}). Results obtained were very satisfactory.

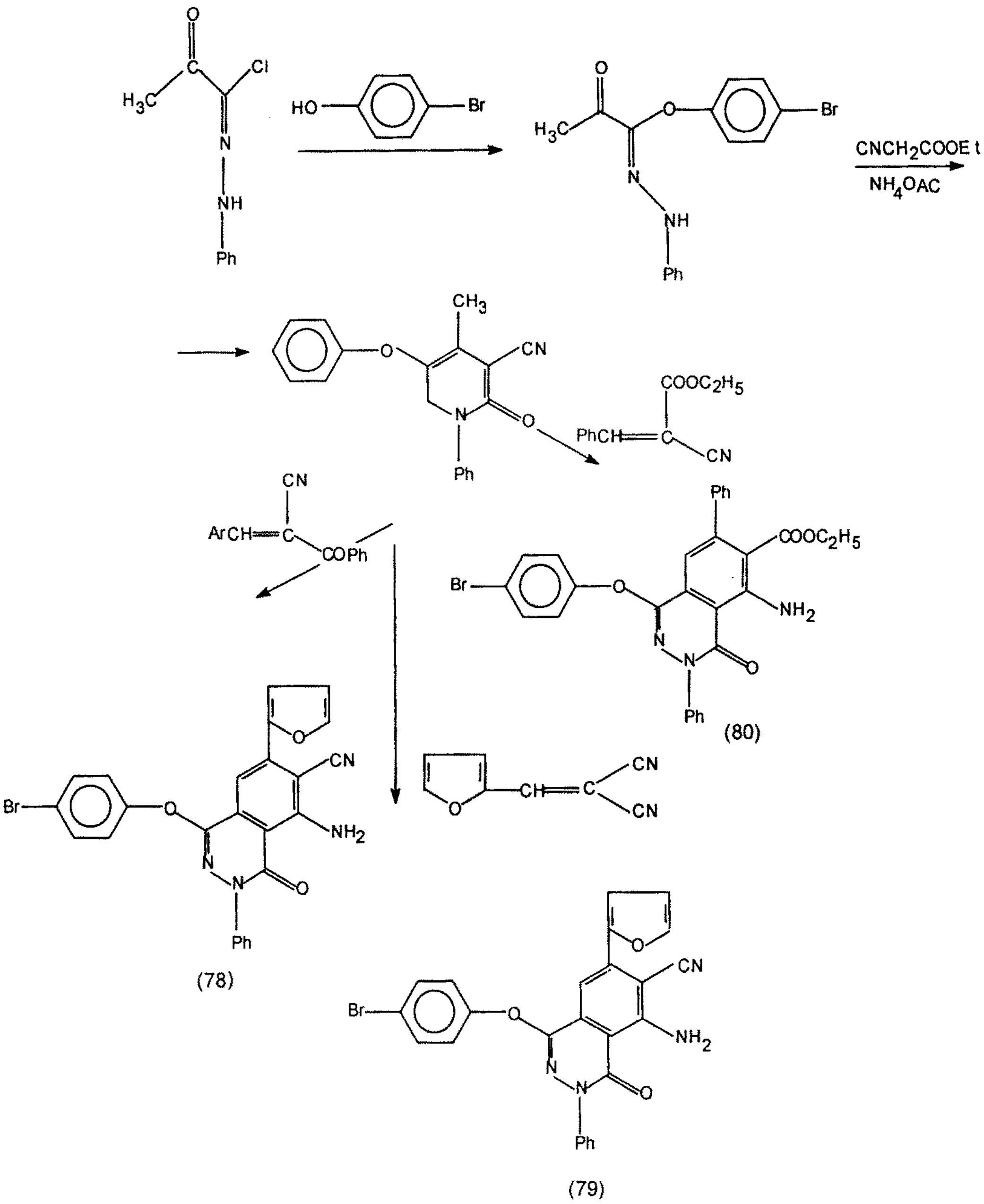
A novel biosensor system for cyanide based on a chemiluminescence reaction was reported by Kazunori and his collegues.[104] A highly sensitive biosensor system was developed to detect CN, based on the rhodinase-sulfite oxidase reaction and subsequent luminol chemiluminescence reaction.

Synthesis and relation between the antimicrobial activity and dipole moment of some phthalazinone derivatives were reported by Kassim and Co-workers.[105] They prepared three new series of phthalazinone derivatives from 4-hydroxy-2-phenylphthalazin-1(2H)-one(1). The biological activity of these compounds have been tested against gram positive and gram negative bacteria, yeast and fungi using diffusion method. The minimum inhibitary action (MIC) has been determined for biological active compounds. From the static dielectric constant measurements, the dipole moment has been calculated and its relation with the biological activity has been determined which gave a contravarient correlation.

Chemiluminescent reagents for determining peroxidase in clinical analysis were reported by Makota and Co-workers.[106] One of the chemiluminescent reagent for determining peroxidase in clinical solutions is a combination of a) 2,3-dihydro-1,4-phthalazinedione compound, b) a chemiluminescent enhancer, c) an oxidant, and d) a chelating agent.

Spectroscopic and magnetic properties of the dimeric (Cu(SO$_4$)$\cdot$ 1,4-dihydrazinophthalazine)$\cdot$$H_2O_2$ complex were reported by David L. and coworkers.[107]

A novel synthesis aryloxypyridazines, phthalazines and thieno-[3,4-d] pyridazine derivatives were reported by Ibrahim and Co-workers.[108] The reaction of hydrazidoyl chloride with *p*-bromophenol afford the ether derivative which on treatment with ethyl cyanoacetate furnish 6-(4-bromophenyloxy)-4-lyamino-2,3-dihydro-5-methyl-2-phenyl-3-puridazinone. This compound is then utilized to synthesize a variety of heterocyclic compounds such as phthalazine derivatives, (78, 79 and 80).



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Call, Hans Peter[109] reported enzyme containing bleaching composition for ligneous material and its applications. In presence of phthalhydrazide and laccase improves bleaching power.

A new method for the syntesis of 1-arylphthalazine was reported by S. Shahikant and Co-workers.[110] A simple versatile method for the conversion of 1-aroyl-2-(substituted benzididene) hydrazine to 1-aryl-phathalazines using polyphosphate ester has been reported.

Importance of the present work

The phthalazine derivatives have attracted the attention because of their therapeutic values. A number of phthalazyl hydrazines in particular are apparently true hypotensive agents of mild potency and reasonably safety.

It has been reported that 1-isoamyloxy-3-phenyl-4-keto-3,4-dihydrophthalazine is more effective than streptomycin or dihydrostreptomycin in the *in VIVO* treatment of tuberculosis in mice. 1-(2-Aminoethylamino)-4-(*p*-chloroanilino) phthalazine displays slight antimalerial activity against avian maleria. Certain 2-phenyl-4-hydroxy-phthalazones have shown high tuberculostatic activity against *Mycobacterium tuberculosis* both in *Vitro* and in *Vivo*.

Many phthalazines when oxidized in the cold with alkaline oxidants exhibit striking chemiluminescence. This property of phthalazines is used for the detection of specific nucleic acid or protein in a sample. Chemiluminescent property of luminol was used for determining total organic carbon (TOC) in water and for determining antioxidant activity of drugs. Chemiluminescent reactions of luminol were used for the development of novel biosensor system for cyanide. Phthalazine chemiluminescent reagents are used for determining peroxidase in clinical analyses.

As mentioned earlier a large number of phthalazine derivatives have been found to possess diverse biological and chemiluminescent activities. Evaluation of the antimicrobial potential of the newly synthesized compound is an important step in the development of the drug that may be effective against microbial infections and less toxic to the host.

Thus, taking into consideration commendable medicinal importance, the problem on the synthesis of some new biological active compounds has been undertaken. The present work involves the synthesis of some new phthalazine derivatives and testing them for their microbiological activities. These compounds are expected to exhibit promising anti-microbial activities.