# SEARCH FOR BIOLOGICALLY ACTIVE SUBSTANCES AMONG HETEROAROMATIC COMPOUNDS (REVIEW)

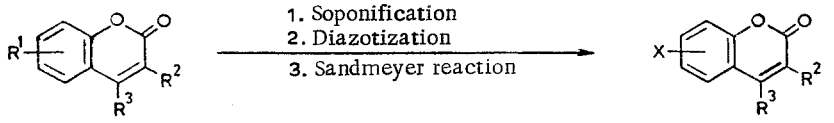
N. V. Subba Rao*

UDC 541.69:547.7/8

Research on the synthesis and investigation of the chemical and spectral characteristics of heterocyclic compounds carried out in the department of chemistry Osmania University (Hyderabad, Andra Pradesh, India) is examined in the review.

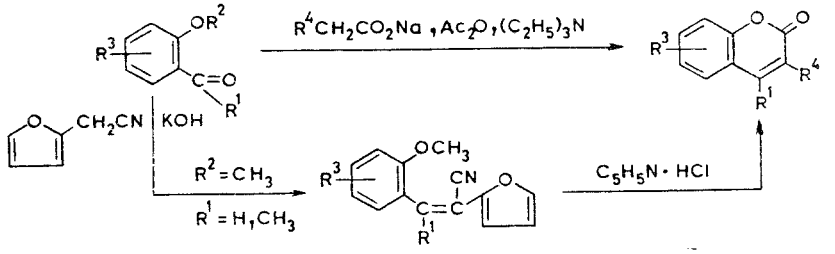
Our interest in benzopyrones was associated with the fact that they obtain the α,β-unsaturated carbonyl system that is assumed to be responsible for the biological activity of the natural pesticides rotenone and pyrethrin. The research in this direction was begun two decades ago in order to ascertain the chemical-biological principles in the benzopyrone series and to obtain selective and low-toxicity insecticides.

Benzo-α-pyrones. A number of amino- [1], halo- [2, 3], and nitro-substituted coumarins [4] have been obtained by known methods. It has been established that the activity of 3-phenylcoumarins increases considerably when there is a bromine atom in the 7 position and a methyl group in the 4 position. A novel feature in these syntheses was the successful application of the Sandmeyer reaction for the preparation of the halo derivatives.




$R^1$ = 4- or 5-NHAc; $R^2$ = H, $C_6H_5$, CN; $R^3$ = H, $CH_3$; X = 6- or 7-Cl, Br

Subsequently, 3- and 4-hetarylcoumarins were obtained [5-7]. 7-Bromo-3-(3-pyridyl)-4-methylcoumarin was found to be half as toxic with respect to fish than rotenone.



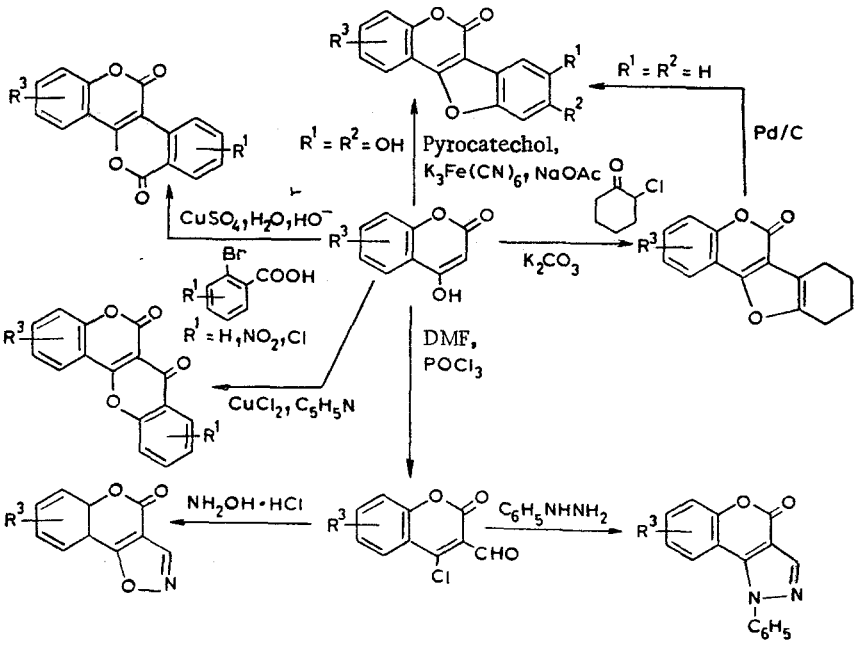

$R^1$ = H, $CH_3$, 2-furyl; $R^2$ = H; $R^3$ = NHAc, $NH_2$, Hal, $NO_2$, $CH_3$, OH, $OCH_3$;
$R^4$ = 2-furyl, 3-pyridyl, 3-indolyl

The 4-hydroxycoumarin ring attracted attention as a bearer of biological activity and from the point of view of biogenesis immediately after the detection of the strong anticoagulant activity of dicumarol and the biogenetic relationship between 3-phenyl-4-hydroxycoumarins and coumestanes and isoflavonoids. In addition, the 4-hydroxycoumarin ring is present in the antibiotics novobiocin and coumermycins. On the basis of 4-hydroxycoumarin we developed new methods for the preparation of various heterosystems condensed with coumarin in the 3 and 4 positions, among which a search was made for new anticoagulants and anti-

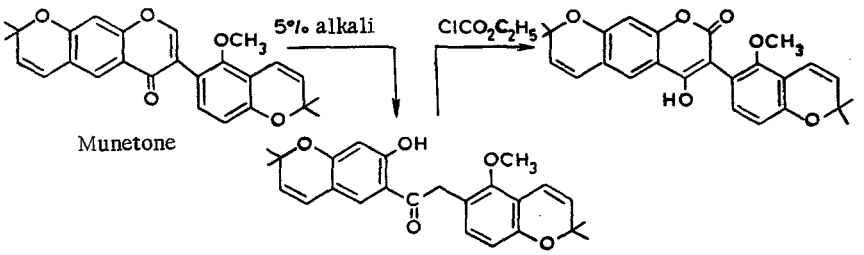
*Deceased.

Osmania University, Hyderabad 500007. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 291-310, March, 1977. Original article submitted March 29, 1976.

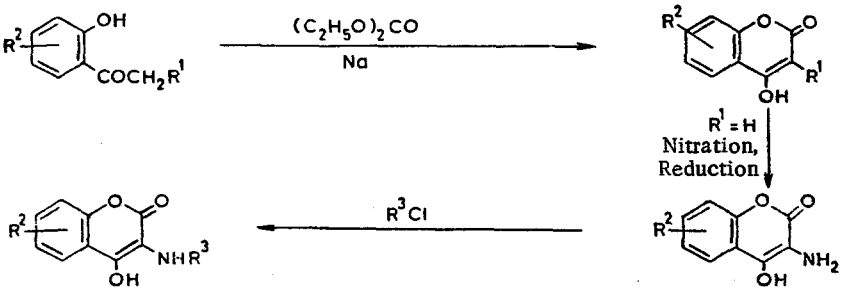
bacterial and fungicidal agent [8-10].




Scandenine and lonchocarpic acid, found in *Derris scandens*, a plan with insecticidal properties, are 3-aryl-4-hydroxycoumarins [11]. Isoflavonoids isolated from plants (munetone, for example) on treatment with alkali gave desoxybenzoins, which are converted to 3-aryl-4-hydroxycoumarins by the Gilbert–MacGoochan method [12].




In addition, 3-aryl-4-hydroxycoumarins with a resorcinol or phloroglucinol ring as the A ring were synthesized from the corresponding desoxybenzoins [12]. Some amino-, halo-, and nitro-substituted 3-phenyl-4-coumarins were obtained by the Boyd–Robertson method [13].

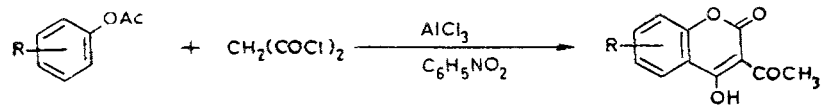



$R^1 = C_6H_5, H$; $R^2$ = 7-OH, 7-$OCH_3$, NHAc, $NH_2$, 5,7-$(OH)_2$, 5,7-$(OCH_3)_2$, 6-NHAc, 6-$NH_2$

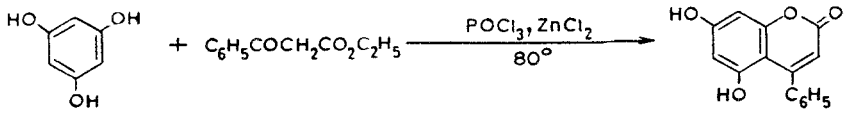
$R^3$ = Alkyl, aryl, hetaryl, acyl

3-Amino-4-hydroxycoumarins [14] and their N-alkyl, N-aryl, and N-acyl derivatives, which were obtained as novobiocin analogs, have high antibacterial activity.

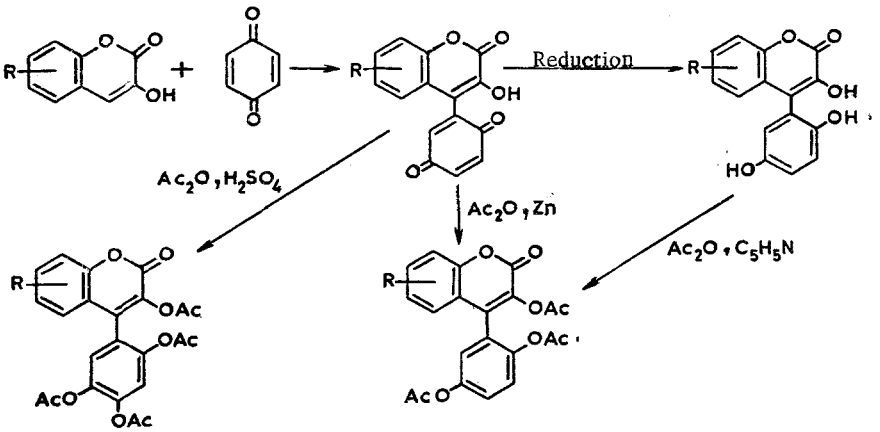
3-Acyl-4-hydroxycoumarins, which contain a triketo system, are strong antibacterial and fungicidal agents. The preparation of these compounds [15] from phenyl esters of acetic acid and malonyl chloride in one step is a new convenient synthesis.



An oil, from which a number of 4-phenylcoumarins could be isolated, was obtained from the extract of the plant *Messua ferrea*, which is widespread in India. For the search for new antitumorigenic agents we decided to synthesise 4-phenylcoumarins with substituents in both the 4-phenyl and A rings. 4-Phenyl- and 4-phenyl-3-methylcoumarins [16], as well as 4-phenylcoumarins fused in the 7 and 8 positions with furan and α- and γ-pyrone systems were obtained by condensations of the Pechmann or Perkin type.

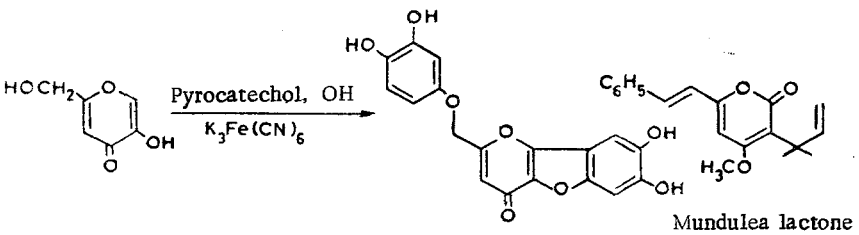


The synthesis of various 4-(hydroxyaryl)-3-hydroxycoumarins [17] with potential fungicidal activity was recently developed on the basis of condensation of 3-hydroxycoumarins with benzoquinone.



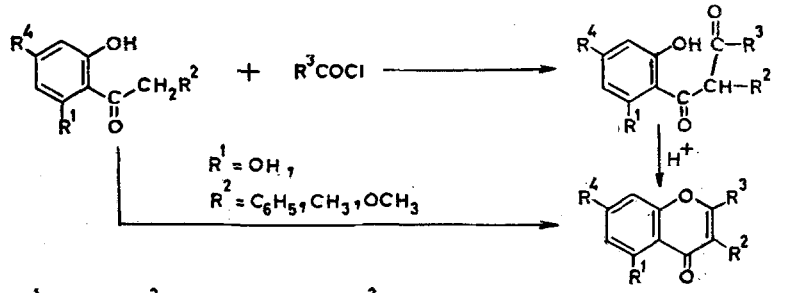
γ-Pyrone Derivatives. The isolation [18] of a lactone from *Mundulea suberosa* in our laboratory served as an impetus for the synthesis of a number of similar compounds. The oxidative condensation of kojic acid with pyrocatechol led [19] to the compound indicated in the following scheme.

Chromones containing various substitutents in the 2 and 2,3 positions, as well as amino and hydroxyl groups in the A ring, were obtained by means of a modified Baker–Venkataraman method [20-25]. 2,4-Dihydroxy-, 2,4,6-trihydroxy-, and 4-amino-2-hydroxyacetophenones with substituents ($C_6H_5C_6H_4$, $CH_3$, and $OCH_3$) in the ω position were condensed



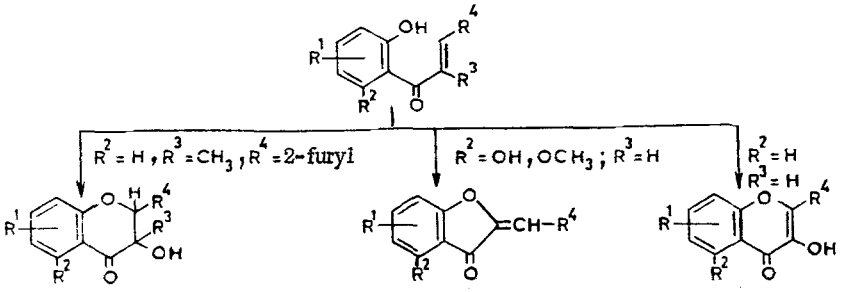

Mundulea lactone

with aromatic and heteroaromatic acid chlorides in refluxing acetone in the presence of anhydrous potassium carbonate. In this one-step variant of the Baker–Venkataraman synthesis, ω-unsubstituted, 2,4-dihydroxyacetophenones gave β-diketones, which were subsequently cyclized to flavones in the presence of protic acids, whereas both unsubstituted and substituted 2,4,6-trihydroxyacetophenones immediately gave chromones. The 7-amino-flavones obtained by the same method were converted to 7-chloro- and 7-bromoflavones via the Sandmeyer reaction. This method was found to be better than the synthesis of 2-chloro(bromo)-2-hydroxyacetophenones by the Baker–Venkataraman method.




$R^1 = H, OH$; $R^2 = C_6H_5, CH_3, OCH_3$; $R^3 = C_6H_5, p\text{-}C_6H_4OCH_3$, 2-furyl, $C_6H_3(OCH_3)_2\text{-}3,4$, $C_6H_2(OCH_3)_3\text{-}3,4,5$; $R^4 = OH, NH_2, Cl, Br$.

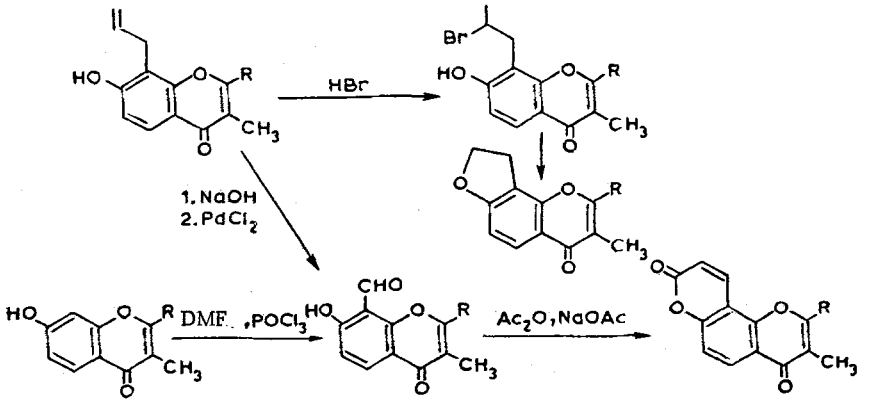
It is known that 7-aminoflavone is an antituberculous agent and also that an amino group and halogen are present in many physiologically active compounds. In addition, 2-hetaryl-chromones [for example, 6-chloro-2-(2-quinolyl)chromone] display considerable activity against sarcoma-180. In this connection, 2-heteryl- or 2-aryl-3-methoxychromones with halogen or an amino group in the benzene ring were synthesized by oxidation of the corresponding chalcones. Whereas chalcones without a substituent in the 6 position gave 3-hydroxychromones on oxidation with alkaline hydrogen peroxide, 6-substituted chalcones were converted to a mixture of 3-hydroxychromones and five-membered coumarins [26-29]. Under the reaction conditions, α-methyl-2-hydroxyfurfurylideneacetophenone gave 2-(2-furyl)-3-methyl-3-hydroxychromone with 2-H and the 3-hydroxy group in a cis orientation [26].

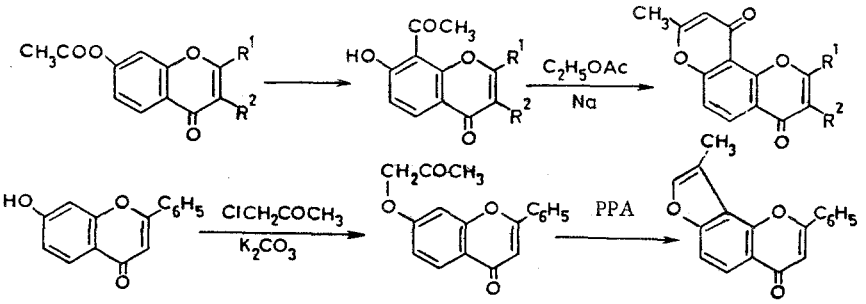



At the same time, 2-hydroxychalcones containing another substituent only in the 6 position were oxidized by manganese (III) acetate only to 3-coumarones.

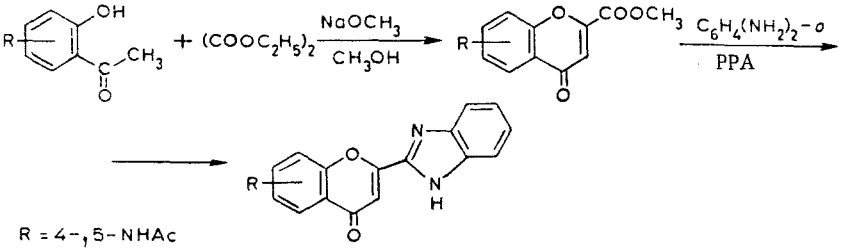
Protection of the free hydroxyl groups by benzylation made it possible to raise the yields of coumarones [30]. It should be noted that 3-coumarones with a resorcinol system in the A ring were obtained for the first time.

Several 3-alkylchromones condensed in the 7,8 positions with furan and α- or γ-pyrone rings were obtained to expose the effect of a "built-on" ring on the toxicity with respect to fish [31, 32].

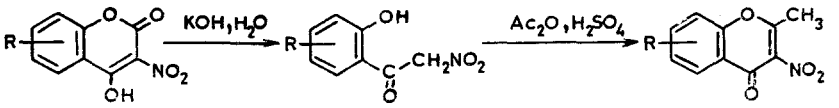




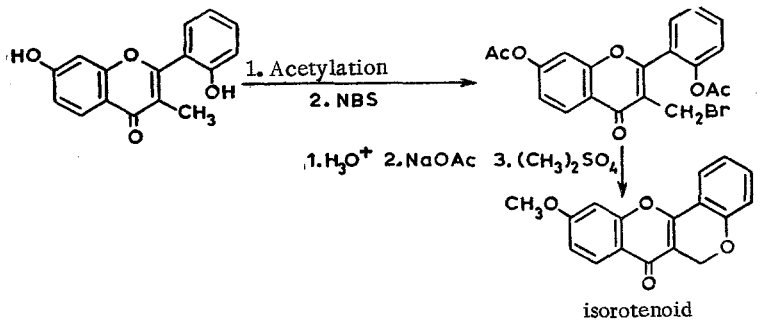
The condensation of 2-methoxycarbonylchromones with o-phenylenediamine in the presence of polyphosphoric acid (PPA) led to the formation of benzimidazoles [33], whereas the reaction (Claisen) with aliphatic acid esters gave 2-alkylchromones [34].



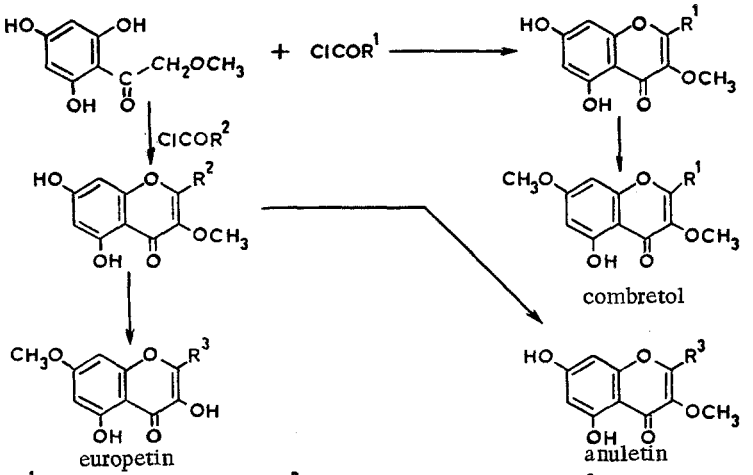
It has been reported that α-nitrocarbonyl compounds have antihistamine activity. It was recently established that ω-nitro-2-hydroxyacetophenones undergo an interesting C-acylation reaction at the active methylene group with subsequent cyclization to the previously unknown 2-methyl-3-nitrochromones [35].



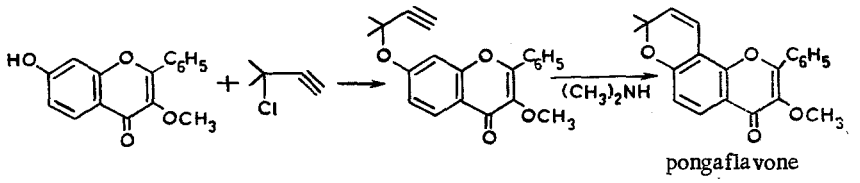
Gribbs and Ollis have postulated the biogenesis of rotenoids from isorotenoid precursors. To verify this hypothesis we synthesized an isorotenoid that is suitable for subsequent conversion to the rotenoid skeleton [36]. It is possible that compounds with isorotenoid structures exist in nature.



Synthesis of Some Natural Substances. Various myricetin derivatives such as combretol (from the seeds of *Combretum*), anuletin (from the leaves of *Aegialitis*), and europetin (from the leaves of *Plumbago*) have been isolated from plants. Combretol, which is partially methylated myricetin, was obtained by partial methylation of 5,7-dihydroxy-3.3'4',5'-tetramethoxyflavone. Anuletin and europetin were synthesized from 5,7-dihydroxy-3-methoxy-3',4',5'-tri-O-benzylflavone [25].

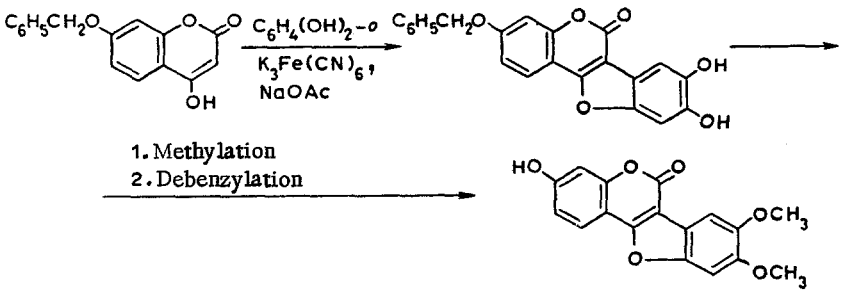



Pongaflavone, isolated from the bark of *Pongamia glabra*, was assigned the 2",2"-dimethylpyrono[5',6':7,8]-3-methoxyflavone structure,

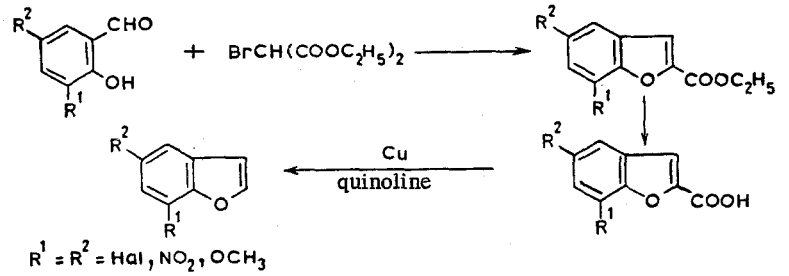



which was confirmed by synthesis from 7-hydroxy-3-methoxyflavone [37].

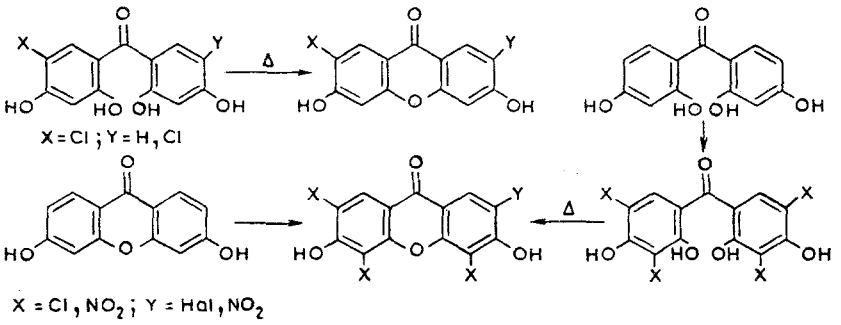
The 7-hydroxy-11,12-dimethoxycoumestane structure was proved for the coumestane isolated from alfalfa [38]. This compound was synthesized by oxidative condensation of 7-benzyloxy-4-hydroxycoumarin with pyrocatechol [39].



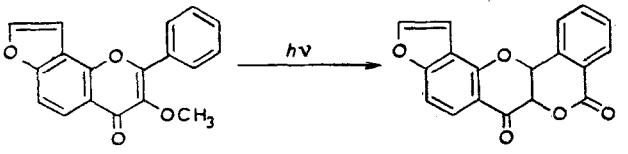

Coumarones. The condensation of substituted salicylaldehydes with bromomalonic ester in the presence of anhydrous potassium carbonate and subsequent hydrolysis and decarboxylation led to halo-, nitro-, and methoxy-substituted benzofurans [40, 41].



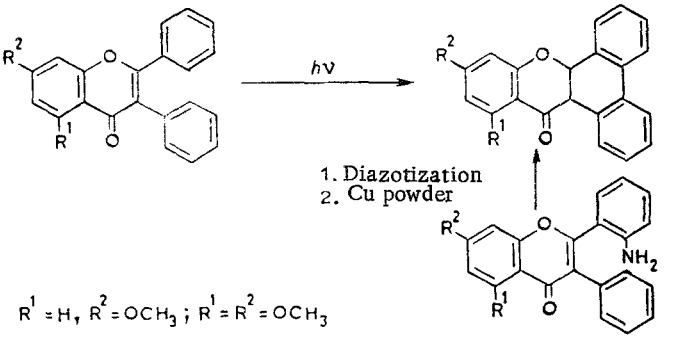
Xanthones. The condensation of resorcinol or 4-chlororesorcinol with chloro-substituted β-resorcylic acids gave the corresponding tetrahydroxybenzophenones, which can be cyclized to 3,6-dihydroxyxanthones. A number of halo- and nitro-3,6-dihydroxyxanthones were obtained by direct halogenation and nitration of the xanthones themselves or the intermediate benzophenones [42].



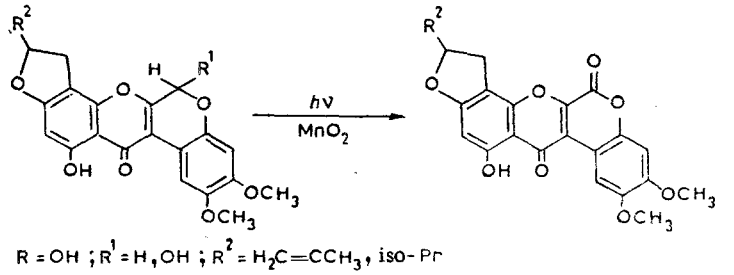

Photochemical Transformations of Heterocyclic Systems. Karanjin, one of the main flavones of the seeds of *Pongamia glabra*, has insecticidal properties. A five-ring compound is formed when methanol solutions of karanjin are irradiated (350 nm) [43].



Irradiation of 2,3-diphenylchromones similarly leads to the corresponding phenanthrochromones [44].



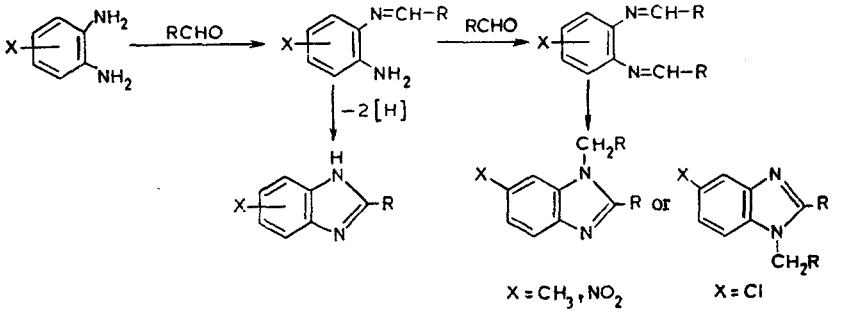

It is known that irradiation of flavonoids leads to various transformations of the cyclic system. In this connection, the photochemistry of villosol and related compounds was studied. The structures of the photolysis products were confirmed by oxidation of the starting substances [45].



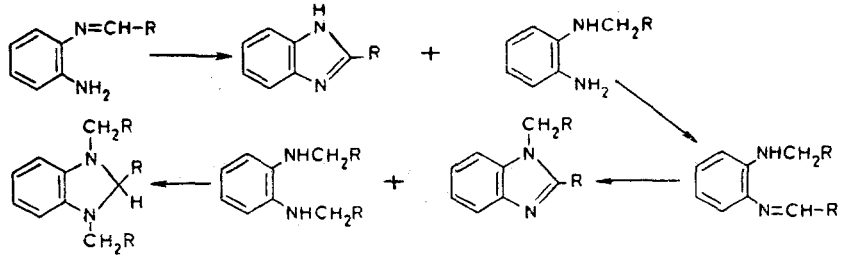
Formation of Nitrogen Heterocycles from O-Diamines and Carbonyl Compounds and Their Thermal Stabilities. The reaction of o-diamines with carbonyl compounds has been investigated in detail for two reasons. First, it is the principal method for the synthesis of imidazole derivatives that are undergoing intensive study to find antihistamine, antibacterial, and fungicidal agents and vitamin B analogs. Second, this reaction opens up extensive possibilities for the study of the mechanisms of the formation of heterocycles. In our laboratory we undertook a systematic study of the reaction of o-phenylenediamines with aldehydes and ketones, during which particular attention was directed to the thermal stabilities of the reaction products.

The course of the reaction and the ease of the formation of benzimidazole from unsubstituted o-phenylenediamines and aromatic aldehydes in acetic acid were studied in detail [46-50]. The condensation of unsubstituted o-phenylenediamine with alkyl-, halo-, alkoxy-, or nitro-substituted aldehydes leads to 2-substituted benzimidazoles. Hydroxy and amino aldehydes give exclusively 1,2-disubstituted benzimidazoles. It is assumed that the formation of benzimidazoles proceeds through intermediate mono- and dianils. When there is a chlorine atom or a nitro group in the 4 position of the diamine, the yield of 2-substituted benzimidazole increases, and this constitutes evidence for the significant role of the substituent in the diamine molecule. The cyclization of dianils formed from 4-substituted o-phenylenediamines may give two isomeric 1,2-substituted benzimidazoles.

A comparison of the condensation products with authentic samples proved that 4-methyl- and 4-nitrophenylenediamines give 1,2,6-trisubstituted benzimidazoles, whereas 4-chlorophenediamine gives 1,2,5-trisubstituted benzimidazoles.



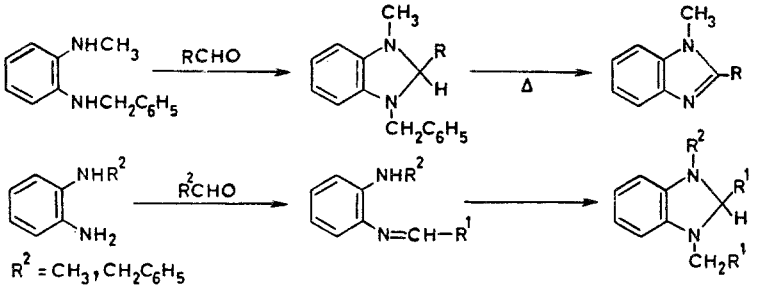

In addition to the benzimidazoles indicated above, the formation of small amounts of yet a third compound was observed in some reactions, for example, in the reaction of o-phenylenediamine with benzaldehyde [46] and m-nitrobenzaldehyde [47] and of 4-methyl-o-phenylenediamine with benzaldehyde and p-methoxy- and m-nitrobenzaldehyde [48, 49]. The substance obtained from o-phenylenediamine and benzaldehyde was found to be identical to the compound previously described as a diazepine [51]. However, a spectroscopic study of these compounds showed that they are actually 1,2,3-trisubstituted benzimidazolines [52, 53]. A mechanism including successive processes involving oxidation—reduction of the intermediate monoanils has been proposed for the formation of 1,3-dibenzyl-2-phenylbenzimidazoline [54]. This benzimidazoline was also obtained directly from N,N'-dibenzyl-o-phenylenediamine and benzaldehyde.



The ease of formation of benzimidazoline in the latter reaction complelled us to extend this synthesis to other aldehydes for the subsequent study of the thermal stabilities of the resulting benzimidazolines [52]. Pyrolysis [55] of the benzimidazolines at 200° in inert and ordinary atmospheres led to 1-benzyl-2-arylbenzimidazoles, which were also obtained for structural proof from N-benzyl-o-phenylenediamine and the corresponding aldehyde. A detailed study [56] of pyrolysis with various catalysts with the application of gas–liquid chromatography (GLC) for analysis of the cleavage products showed that the reaction has a purely radical mechanism.

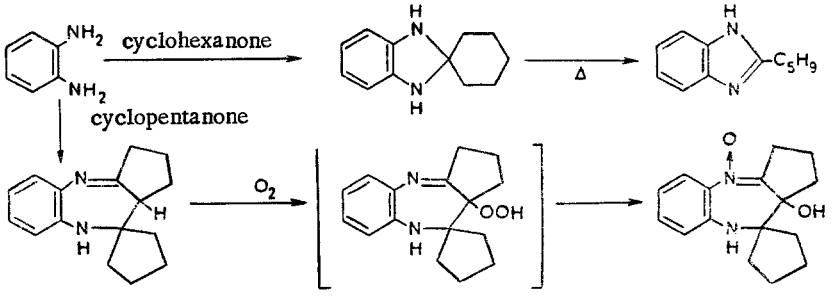
It was also found that 1-benzyl-2-aryl-5-chlorobenzimidazoles are formed when there is a chlorine atom in the 5 position [57], whereas 1-benzyl-2-aryl-6-methylbenzimidazoles are formed when there is a methyl group in the 5 position. The difference in the thermal or thermodynamic stabilities probably determines the formation of one or the other isomer, all other things being equal.

Benzimidazolines with different substituents attached to 1-N and 3-N were also obtained, since one might have expected that the study of the pyrolysis of these compounds would assist one in arriving at a better understanding of the reaction mechanism [58]. With this end in mind we studied three series of compounds: 1-methyl-2-aryl-3-benzyl-, 1-methyl-2-aryl-3-(substituted benzyl)-, and 1-benzyl-2-aryl-3-(substituted benzyl)-benzimidazolines. Whereas 1-methyl-2-aryl-3-benzylbenzimidazolines were formed as a result of direct condensation of N-Methyl-N'-benzyl-o-phenylenediamine with aromatic aldehydes, it was necessary to obtain 1-methyl-2-aryl-3-(substituted benzyl)benzimidazolines by disproportionation of the corresponding N-methyl(or benzyl)-N'-arylidene-o-phenylenediamines.

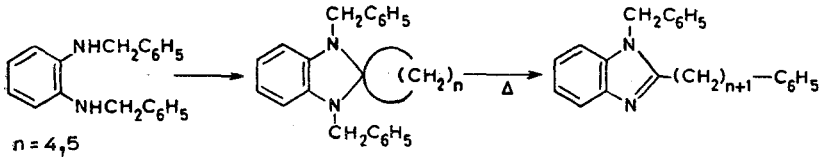



Pyrolysis of 1-methyl-2-aryl-3-benzylbenzimidazolines gave 1-methyl-2-arylbenzimidazoles, and this provides evidence that the benzyl group is detached from the nitrogen atom, probably because of resonance stabilization of the benzyl radical. Pyrolysis of 1,3-dibenzyl-2-arylbenzimidazolines in which substituted (R') or unsubstituted (R) benzyl groups are attached to the nitrogen atoms showed that it is precisely the stability rather than the volume of the group split out that determines the direction of the reaction. When the stabilities of R and R' are comparable, both groups are split out during pyrolysis; however, if the difference in the stabilities is considerable, the more stable group is primarily eliminated. Substitution in the 5 position of benzimidazolines does not change the direction of pyrolysis [59].

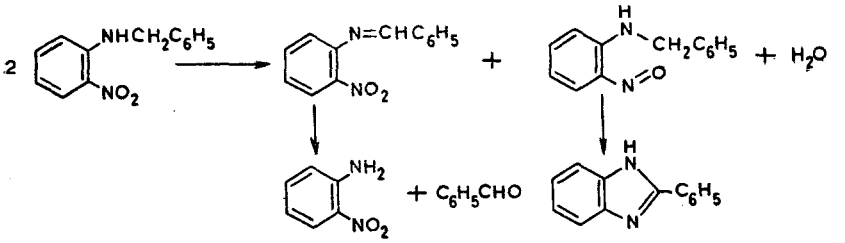
The condensation of cyclohexanone with o-phenylenediamine led to a spiro compound, which underwent isomerization to 2-pentylbenzimidazole on heating in diphenyl ether [60]. The same condensation with cyclopentanone gave a new diazepine derivative, for which the 2,3-cyclopentano-3,4-dihydro-(5H)-1,5-benzodiazepine-4-spirocyclopentane structure was proved by spectroscopic and chemical methods [61]. Compounds of the same type are formed with cycloheptanone [62]. A new reaction proceeding through a step involving hydroxylation to give an N-oxide was observed in the oxidation of the diazepine obtained from cyclopentanone.



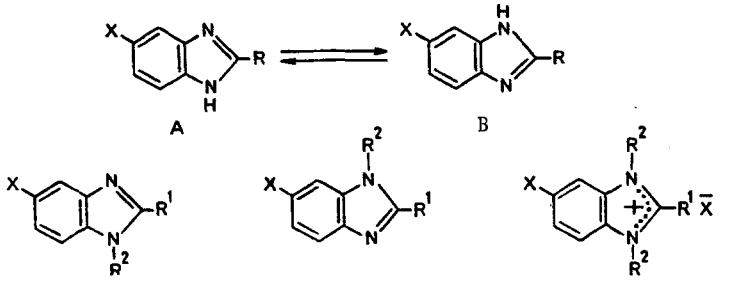
The reaction of N,N'-dibenzyl-o-phenylenediamine with ketones also leads to spiro compounds, which undergo isomerization to benzimidazoles when they are heated [62].



Reaction of o-Chloronitrobenzene with Benzylamine. In the course of a study of the formation and reactivity of the benzimidazole system we carried out the condensation of o-chloronitrobenzene with benzylamine at 200°, as a result of which, in addition to the expected benzylamino derivatives, we obtained 2-phenylbenzimidazoles as the chief product [63]. The intermediate N-benzyl-o-nitroaniline was heated at 220° for 1 h to ascertain the mechanism of the formation of the benzimidazole. 2-Phenylbenzimidazole, o-nitroaniline, and benzaldehyde were isolated from the reaction mixture. The possible reaction mechanism is depicted by the following scheme.



Substitution at the Nitrogen Atom in Tautomeric Benzimidazoles. Benzene-ring-substituted benzimidazoles having a free NH group can exist in the form of two tautomers. As a result of alkylation, 5(6)-substituted benzimidazoles may give 1,5- and(or) 1,6-disubstituted benzimidazoles. Quaternization of these isomeric benzimidazoles leads to the same compound.



The methylation of benzimidazoles (X = $CH_3$, Cl, $NO_2$; R = H, $CH_3$, $C_6H_5$) with 1 mole of methyl iodide was carried out by heating the benzimidazole in refluxing acetone in the presence of anhydrous potassium carbonate. The benzimidazoles were benzylated smoothly by the method in [64] by heating with an equimolar amount of benzyl chloride in the presence of fused sodium acetate and traces of iodine. The structures of the substitution products were proved by comparison with the isomeric benzimidazoles obtained by unambigous methods [65]. Benzylation of 2-phenyl-5(or 6)-methylbenzimidazole gave only the 1,6 isomer, whereas benzylation of its chloro-substituted analog gave only the 1,5 isomer [64]. However, a mixture (2:1) of the 1,5 and 1,6 isomers was obtained from the corresponding nitrobenzimidazole. A mechanism that takes into account stabilization of the tautomers by inductive and resonance effects and their nucleophilicity was proposed to explain these facts.

Methylation [66] of 5(6)-methylbenzimidazole led to a mixture (1:2) of 1,5 and 1,6 isomers along with a quaternary salt. Considerable amounts of quaternary salts were obtained along with the 1,5 isomers from 2,5(6)-dimethyl- and 2-phenyl-5(6)-methylbenzimidazoles. The 1,6 isomer was formed as the principal or only product in the benzylation of the same three benzimidazoles. These results can be explained by the electron-donor properties of the methyl group, which increases the electron density on the nitrogen atom in the para position relative to it. If the ratio of the isomers obtained can be considered to be a measure

of the relative basicities of the nitrogen atoms, structure A (X = $CH_3$) should be more stable. The formation of the 1,6 isomer can be expected as a result of an $S_E2'$ reaction during attack by the alkylating agent on the tertiary nitrogen atom and subsequent dehydrohalogenation. However, the proposed parallel character of the basicities and nucleophilicities of the nitrogen atoms indicates that tautomer B, which is present in lower concentrations, will undergo more rapid substitution via an $S_E2'$ mechanism. Thus tautomer B, although its concentration is low, may give the 1,5 isomer because of its increased reactivity. In addition, quaternary salts may also be formed from the 1,6 isomer.

The 1,5 isomer was obtained in the methylation [67] of 5(or 6)-chloro- and 2-methyl-5-(or 6)-chlorobenzimidazoles, whereas the 1,5 isomer and the quaternary salts were obtained in different ratios in the methylation of 2-phenyl-5(or 6)-chlorobenzimidazoles. The 1,5 and 1,6 isomers were obtained in ratios of 1:2 and 2:1, respectively in the benzylation of 5(6)-chlorobenzimidazole and its 2-methyl-substituted derivative. Only the 1,5 isomer was obtained in the case of methylation. If the electron-acceptor effect predominates in 5(6)-chlorobenzimidazoles, tautomer B is more stable, and reaction via an $S_E2'$ mechanism leads to the 1,5 isomer. On the other hand, owing to the mesomeric effect of chlorine, tautomer A may prove to be more stable, and this would lead to the 1,6 isomer. One should usually expect the formation of a mixture of 1,5 and 1,6 isomers from 5(6)-chloroimidazoles. Exclusively the 1,5 isomer is obtained in the case of methylation, and this indicates predominance of the inductive effect. The results of benzylation indicate the influence of both the inductive and mesomeric effects.

A mixture of isomers, in which the 1,5 isomer predominated, was obtained in the methylation of 5(6)-nitrobenzimidazoles [68]. This result indicates that an electronegative group stabilizes tautomer B, which gives primarily the 1,5 isomer in substitution. However, the overall deactivating effect of the nitro group lowers the nucleophilicity of the tertiary nitrogen atom in tautomer B, whereas tautomer A, as the doubtlessly more reactive form, can easily ensure the formation of the 1,6 isomer, despite the fact that its concentration is lower.

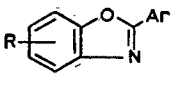
Other Nitrogen-Containing Heterocycles. The spectral characteristics of N-oxides of pyridine, picoline, quinoline, and quinaldine were studied to ascertain the characteristic absorption of the N–O bond and the shift in the absorption band as a function of the solvent [69-71]. The spectral characteristics and complexing capacities of 8-hydroxyquinoline, obtained by an improved method [72], were also studied. The reactivity of the methyl group in picoline and quinaldine N-oxides was investigated [73]. The orientation of electrophilic substitution in 8-hydroxyquinoline N-oxide was studied [74].

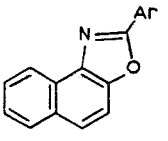
A number of substituted 4-quinazolones were obtained by condensation of N-acylanthranilic acids with primary arylamines [75]. Some 3-aryl-3,4-dihydro-4-quinazolones were prepared from anthranilamide and aromatic aldehydes. Condensation of anthranilamide with aromatic aldehydes in the presence of nitrobenzene, which served as the condensing agent and oxidizing agent, led to 3-aryl-4-quinazolones. All of the synthesized compounds were subjected to screening for fungicidal and antibacterial activity and toxicity with respect to fish. Some of them have considerable toxicity.

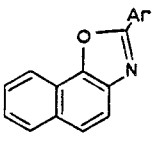
The optimum conditions for the preparation of 2-oxo- and 2-thioxo-4,6-diarylhexahydro-sym-triazines by condensation of benzaldehyde, urea or phenyl-substituted ureas or thiourea, and ammonium acetate in molar ratios of 2:1:1 were worked out.

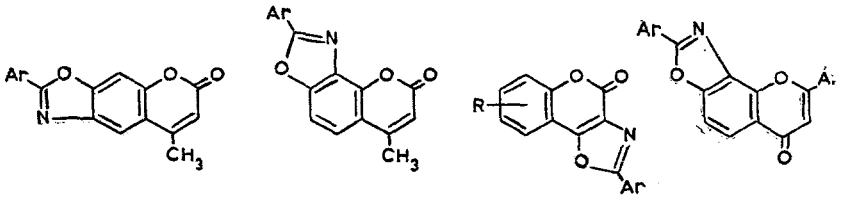
## Heterocycles with Two Different Heteroatoms

Synthesis of Oxazoles, Isoxazoles, and Their Condensed Derivatives. Numerous condensed oxazoles — benzoxazoles [77], naphthoxazoles [78], oxazolocoumarins [79, 80], and oxazoloflavones [81] — were synthesized for screening for antibacterial and fungicidal activity. Particular attention was directed to use of nitrobenzene as a cyclizing agent.



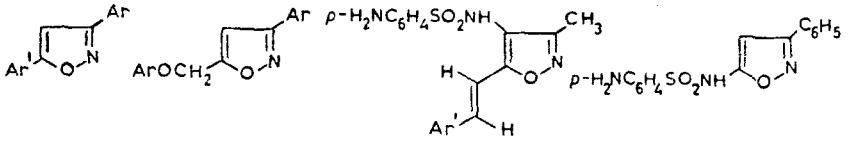





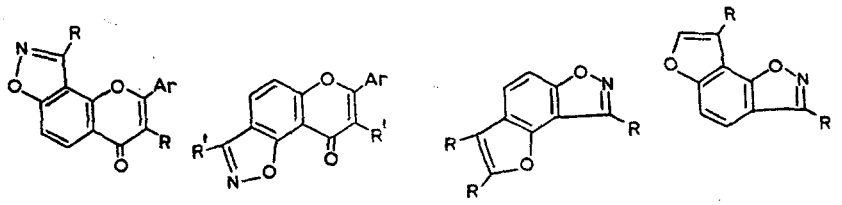
R = halogen $CH_3O$, $CH_3$, $NO_2$, $OCH_2O$
Ar = $C_6H_5$; $C_6H_4Hal$; methoxy-, dimethoxy-, and trimethoxyphenyl; $C_6H_4NO_2$; $C_6H_4NH_2$; methylenedioxyphenyl

A number of 3,5-disubstituted isoxazoles were obtained through chalcone dibromide to study their physical activity [82, 83]. Some compounds of this series were used to establish the direction of enolization of 1,3-diketones by a chemical method. 3-Phenyl-5-aryloxymethylisoxazoles were prepared by condensation of allyl aryl ethers with benzonitrile oxide and subsequent dehydrogenation of the intermediate $\Delta^2$-isoxazolines with N-bromosuccinimide (NBS) [84]. The structures of these compounds were confirmed by unambiguous synthesis from 3-phenyl-5-bromomethylisoxazole and phenols. A number of (3-methyl-5-styryl-4-isoxazolyl)sulfanilamides were obtained by treatment of 4-amino-3-methyl-5-styrylisoxazoles with p-aminobenzenesulfonyl chloride [85]. (3-Aryl-5-isoxazolyl)sulfanilamides were synthesized for comparative study.



Ar = $C_6H_4Hal$, $C_6H_4CH_3$, $C_6H_4OH$, $C_6H_4C_6H_4OH$, hydroxy- or ethoxynaphthyl
Ar′ = $C_6H_4Hal$, $C_6H_4NO_2$, $C_6H_4CH_3$, $C_6H_4OH$, methylenedioxyphenyl, naphthyl, anthryl

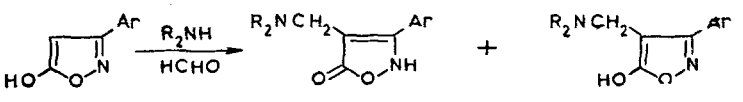
A number of pyranobenzisoxazoles were synthesized from 7-hydroxy-8-acylflavones [86] or 7-acetyl-6-hydroxybenzisoxazoles [87]. Some furobenzisoxazoles [88] and 8-hydroxypyranobenzisoxazoles [89] were also obtained.



Ar = phenyl or substituted phenyl; R = H, Alk, $C_6H_5$; R′ = Alk, OH

Hydroxyaryl-, haloaryl-, and naphthyl-substituted isoxazoles display high antibacterial and fungicidal activity. N′-Isoxazolylsulfanilamides and Mannich bases from 5-isoxazolones were found to be even more active. 3-Aryl-5-aryloxymethylisoxazolones have moderate contraceptive action. Oxazolo- and isoxazolocoumarins and flavones have low activity. Some benzoxazoles have displayed moderate antispasmodic activity.

Reactivities of Isoxazole Derivatives. A number of 3-aryl-5-isoxazolones have been subjected to the Mannich reaction with various alkyl-, aryl-, and hetarylamines for the study of the reactivity of the isoxazole ring. The spectroscopic data provide evidence that the Mannich bases obtained exist in both the 2H and 4H forms [90].



Spectral Studies. The UV spectra of (hydroxyaryl)isoxazoles with aryl and hydroxyl groups in different positions were studied [91].

A new approach was worked out for the elucidation of the direction and degree of enolization of unsymmetrical 1,3-diketones by means of the mass spectra of isoxazoles obtained from these diketones [92].

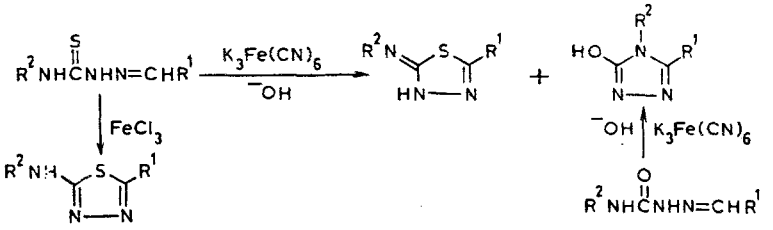
The benzisoxazole ring is extremely stable with respect to electron impact [87, 88]. In a study of the mass spectra of pyrano- and furobenzisoxazoles it was shown that the isoxazole ring is more stable than the γ-pyrone ring but less stable than the furan ring.

It was proved by means of the UV and IR spectra that the 5-styryl derivative rather than the 3 or 3,5 derivative is formed in the condensation of 3,5-dimethyl-4-nitroisoxazole with aromatic aldehydes [93].

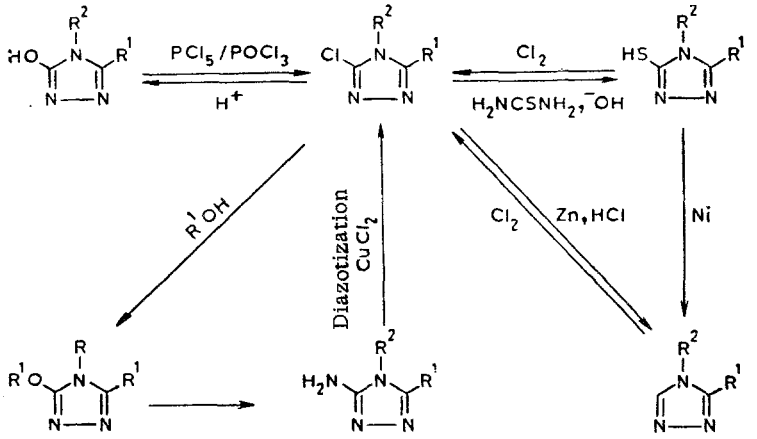
Study of Complexing. 3-o-Isoxazolylphenol [94] and 7-acetyl-6-hydroxy-3-methylbenzisoxazole [95] form complexes with transition metals that are stable in acidic and alkaline media. The stability constants of the corresponding complexes for some metals are higher than for complexes with 8-hydroxyquinoline.

## Chemistry of Some Heterocycles Having More than Two Heteroatoms

Research on the synthesis of heterocycles having more than two heteroatoms was begun [96-98] to verify reports of the loss of antituberculous activity of some substituted thiosemicarbazides during their cyclization. It was shown [99, 100] that there is no direct relationship between the change in the antituberculous activity and the existence of 4-substituted thiosemicarbazones in the open or cyclic form. These studies led to an improved method for the synthesis of 5-arylamino-2-aryl-1,3,4-thiadiazoles [97, 100], 5-arylamino-2-aryl-1,3,4-thiadiazolines [97, 98], and 3,4-disubstituted 5-hydroxy-1,2,4-triazoles [101-103].



The latter compounds were found to be unusually reactive and were subjected to a number of transformations [104].

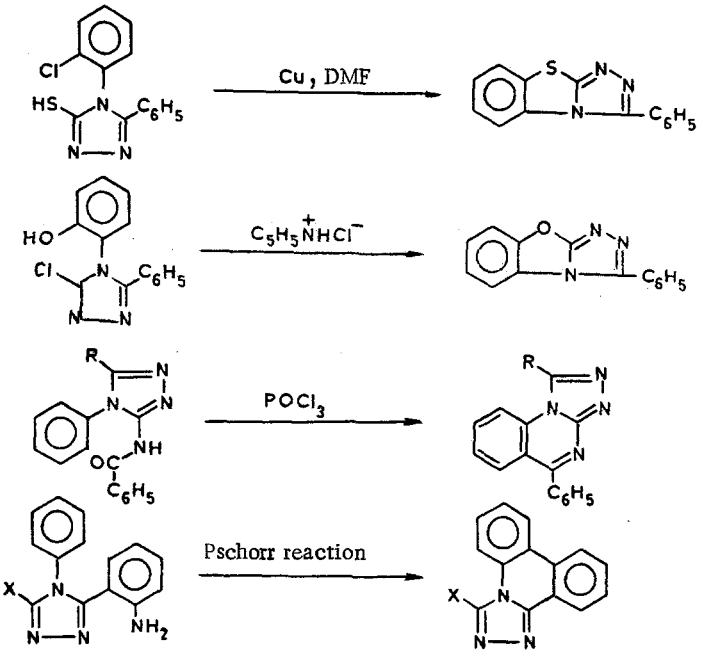


The mass spectra of the compounds described above were recently studied, and some new rearrangements under the influence of electron impact were uncovered [105, 106].

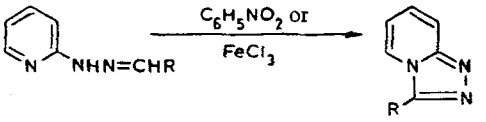
A promising method [107] for the conversion of thiols of the azaheterocyclic series to the corresponding chloro derivatives was developed.

Condensed sym-triazoles were obtained through the appropriate 3,4,5-trisubstituted 1,2,4-triazoles [108].

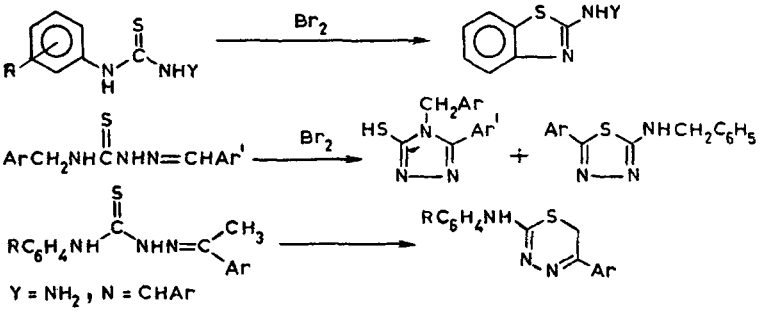
Two methods for the preparation of condensed sym-triazoles were improved [109].




A method for the preparation of 2-amino-5-aryl-1,3,4-thiadiazoles was improved [110], and a method for the direct amination of arylthiadiazoles with hydroxylamine in aqueous sodium hydroxide solution or alcoholic sodium ethoxide solution was found [111].

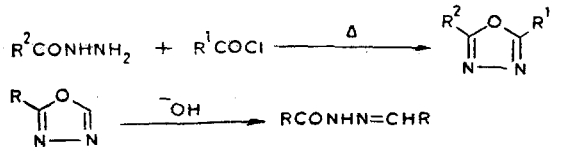



The oxidation of 4-arylthiosemicarbazides and the corresponding thiosemicarbazones with bromine in chloroform gave 2-hydrazinobenzothiazoles or the corresponding hydrazones [112, 113]. Depending on the oxidizing agent, arylaminothiadiazoles or mercapto-sym-triazoles are formed when there is a benzyl group in the 4 position [114, 115].



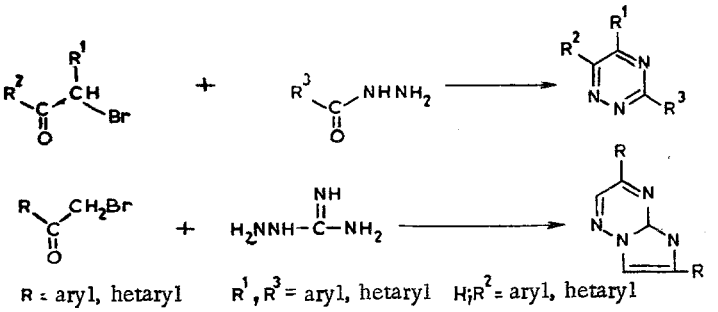

2-Arylamino-5-aryl-6H-1,3,4-thiadiazines were obtained in the oxidation of acetophenone thiosemicarbazones [116].

The continuation of research in this direction led to the development of a convenient method for the synthesis of 2,5-disubstituted 1,3,4-oxadiazoles, which are widely known as scintillators [117]. Monoaryl-1,3,4-oxadiazoles are unstable in alkali and upon hydrolysis form 1-aroyl-2-arylidenehydrazines [118].



The Mannich reaction [119] and nucleophilic substitution [120] in the oxadiazole series, as well as the synthesis of polycyclic oxadiazoles [121] and thiadiazoles [122] based on them, were investigated.

A convenient one-step synthesis of 6-mono-, 3,6-di-, and 3,5,6-trisubstituted 1,2,4-triazines was developed [123, 124]. A number of condensed asym-triazine derivatives — imidazo[1,2-b]-asym-triazines — were obtained by reaction of aryl(hetaryl)-α-halomethyl ketones with aminoguanidine bicarbonate [125].



R = aryl, hetaryl $R^1, R^3$ = aryl, hetaryl $H; R^2$ = aryl, hetaryl

These compounds fluoresce strongly, and their applicability as fluorescing labels in the chemistry of nucleotides and polypeptides is currently under investigation. Some sym-triazolo[3,4-b]benzothiazoles were also obtained, and their chemical and spectroscopic properties were studied [126].

LITERATURE CITED


1. V. Sundaramurthy and N. V. S. Rao, Proc. Indian Acad. Sci., 42A, 249 (1955).
2. V. Sundaramurthy and N. V. S. Rao, Proc. Indian Acad. Sci., 43A, 149 (1956).
3. V. Sundaramurthy and N. V. S. Rao, Proc. Indian Acad, Sci., 54A, 105 (1961).
4. V. Sundaramurthy and N. V. S. Rao. Proc. Indian Acad. Sci., 54A, 321 (1961).
5. B. Sreenivasulu, V. Sundaramurthy, and N. V. S. Rao, Proc. Indian Acad. Sci., 78A, 159 (1973); 79A, 41 (1974).
6. B. Sreenivasulu, V. Sundaramurthy, and N. V. S. Rao, J. Indian Chem. Soc., 51, 488 (1974).
7. N. Someswari and V. Sundaramurthy, Ann. Convention Chem. Soc., Maduri, 52 (1974).
8. D. Malleswar, V. Sundaramurthy, and N. V. S. Rao, Indian J. Chem., 11, 115 637 850 (1973).
9. D. Malleswar, V. Sundaramurthy, and N. V. S. Rao, Proc. Indian Acad. Sci., 80A, 93 (1974).
10. S. R. Moorty, V. Sundaramurthy, and N. V. S. Rao, Indian J. Chem., 11, 854 (1973).
11. C. P. Falshaw, R. A. Harmer, W. D. Ollis, R. E. Wheeler, V. R. Lalitha, and N. V. S. Rao, J. Chem. Soc., C, No. 3, 374 (1969).
12. V. R. Lalitha and N. V. S. Rao, Proc. Indian Acad. Sci., 77, 157 (1973).
13. B. Sreenivasulu, V. Sundaramurthy, and N. V. S. Rao, Proc. Indian Acad. Sci., 80A, 273 (1974).
14. K. S. R. K. M. Rao and N. V. S. Rao, Indian J. Chem., 3, 522 (1965).
15. K. Venkateswara Rao and V. Sundaramurthy, Proc. Indian Acad. Sci., 81A, 118 (1975).
16. M. Subramanyam Raju and N. V. S. Rao, Proc. Indian Acad. Sci., 79A, 223 (1974).
17. N. Someswari, V. Sundaramurthy, and N. V. S. Rao, Unpublished data.
18. N. V. S. Rao, V. R. Lalitha, and G. Srimannarayana, Curr. Sci., 35, 410 (1966).
19. K. R. S. Reddy, G. Srimannarayana, and N. V. S. Rao, Unpublished data.
20. G. Srimannarayana and N. V. S. Rao, Indian J. Chem., 7, 940 (1969); 6, 696 (1968).
21. G. Srimannarayana and N. V. S. Rao, Curr. Sci., 33, 47 (1964).
22. A. V. S. Rao and N. V. S. Rao, Curr. Sci., 35, 149 (1966).
23. M. Vijayalakshmi and N. V. S. Rao, Curr. Sci., 36, 401 (1967); 41, 680 (1972).
24. M. Vijayalakshmi and N. V. S. Rao, Indian J. Chem., 10, 34 (1971).
25. P. N. Sarma, G. Srimannarayana, and N. V. S. Rao, Proc. Indian Acad. Sci., 80A, 168 (1974).
26. A. V. S. Rao and N. V. S. Rao, Curr. Sci., 43, 477 (1974).
27. A. V. S. Rao and N. V. S. Rao, Indian J. Chem., 7, 1091 (1969).
28. P. N. Sarma, G. Srimannarayana, and N. V. S. Rao, Curr. Sci., 39, 133 (1970).

29. K. R. S. Reddy, G. Srimannarayana, and N. V. S. Rao, Proc. Indian Acad. Sci., 81A, 197 (1975).
30. P. N. Sarma, Ph.D. Thesis, Osmania University (1972).
31. A. V. S. Rao and N. V. S. Rao, Proc. Indian Acad. Sci., 80, 102 (1974).
32. G. Srimannarayana, Ph.D. Thesis, Osmania University (1974).
33. K. R. S. Reddy, Ph.D. Thesis, Osmanian University (1973).
34. A. V. S. Rao and N. V. S. Rao, Proc. Indian Acad. Sci., 63A, 24 (1970).
35. K. Venkateswara and V. Sundaramurthy, Annual Convention of Chemists, Roorky University (1975).
36. G. Srimannarayana, J. V. R. Sarma, and N. V. S. Rao, Indian J. Chem., 13, 228 (1975).
37. P. Lakshmi, G. Srimannarayana, and N. V. S. Rao, Indian J. Chem., 13, 228 (1975).
38. R. R. Spencer, B. E. Knuckles, and E. M. Bickoff, J. Org. Chem., 31, 988 (1966).
39. D. Malleshwar, G. Srimannarayana, V. Sundaramurthy, and N. V. S. Rao, Curr. Sci., 36, 346 (1967).
40. A. Annaji Rao and N. V. S. Rao, Unpublished Data.
41. K. Rajeswar Rao and N. V. S. Rao, Proc. Indian Acad. Sci., 58, 336 (1963).
42. K. Rajeswar Rao and N. V. S. Rao, Proc. Indian Acad. Sci., 57, 280 (1963).
43. P. Lakshmi, G. Srimannarayana, and N. V. S. Rao, Indian J. Chem. (in press).
44. K. Prasuna, G. Srimannarayana, and N. V. S. Rao, Annual Convention of Chemists, Madurai (1974).
45. D. Krupadanam, G. Srimannarayana, and N. V. S. Rao, Unpublished data.
46. N. V. S. Rao and C. V. Ratnam, Curr. Sci., 24, 299 (1955).
47. N. V. S. Rao and C. V. Ratnam, Proc. Indian Acad. Sci., 43, 173 (1956).
48. N. V. S. Rao and C. V. Ratnam, Proc. Indian Acad. Sci., 44, 331 (1956).
49. N. V. S. Rao and C. V. Ratnam, Proc. Indian Acad, Sci., 45, 253 (1957).
50. N. V. S. Rao and C. V. Ratnam, Proc. Indian Acad. Sci., 47, 77 81 (1958); 48, 256; 49, 193 (1959).
51. S. Weil and H. Marcinkowska, Roczn. Chem., 14, 1312 (1932); Chem. Abstr., 29, 6233 (1935).
52. V. Veeranagaiah, C. V. Ratnam, and N. V. Subba Rao, Indian J. Chem., 6, 279 (1968).
53. V. Veeranagaiah, C. V. Ratnam, and N. V. Subba Rao, Indian J. Chem., 8, 790 (1970).
54. V. Veeranagaiah, C. V. Ratnam, and N. V. Subba Rao, Indian J. Chem., 10, 133 (1972).
55. V. Veeranagaiah, C. V. Ratnam, and N. V. Subba Rao, Indian J. Chem., 7, 776 (1969).
56. V. Veeranagaiah, C. V. Ratnam, and N. V. Subba Rao, Indian J. Chem., 12, 346 (1974).
57. V. Veeranagaiah, C. V. Ratnam, and N. V. Subba Rao, Proc. Indian Acad. Sci., 79, 230 (1974).
58. P. Satyanarayana Reddy, V. Veeranagaiah, and C. V. Ratnam, Proc. Indian Acad. Sci., 81, 124 and 132 (1975).
59. C. V. Chalapathi Rao and N. V. Subba Rao, Unpublished data.
60. P. Satyanarayana, C. V. Ratnam, and N. V. Subba Rao, Indian J. Chem., 10, 240 (1972).
61 P. Satyanarayana Reddy, C. V. Ratnam, and N. V. Subba Rao, Indian J. Chem., 10, 982 (1972).
62. P. Satyanarayana Reddy, C. V. Ratnam, and N. V. Subba Rao, Unpublished data.
63. C. V. Chalapathi and N. V. Subba Rao, Curr. Sci., 43, 43 (1974).
64. N. V. Subba Rao and C. V. Ratnam, J. Chem. Soc., No. 10, 3087 (1959).
65. N. V. Subba Rao, C. V. Ratnam, and K. Kondal Reddy, Indian J. Chem., 1, 96 (1963).
66. N. V. Subba Rao and K. Kondal Reddy, Proc. Indian Acad. Sci., 70, 81 (1969).
67. N. V. S. Rao and K. Kondal Reddy, Proc. Indian Acad. Sci., 70, 292 (1969).
68. N. V. S. Rao and K. Kondal Reddy, Proc. Indian Acad. Sci., 71, 141 (1970).
69. K. Ramaiah and V. R. Srinivasan, Curr. Sci., 27, 340 (1958).
70. K. Ramaiah and V. R. Srinivasan, Proc. Indian Acad. Sci., 50, 213 (1959).
71. K. Ramaiah and V. R. Srinivasan, J. Sci. Indian Res., 21C, 70 (1962).
72. K. Ramaiah and V. R. Srinivasan, Proc. Indian Acad. Sci., 55, 360 (1962).
73. K. Ramaiah and V. R. Srinivasan, Indian J. Chem., 1, 351 (1963).
74. K. Ramaiah and V. R. Srinivasan, Indian J. Chem., 6, 635 (1968).
75. S. K. V. Seshavataram and N. V. Subba Rao, Proc. Indian Acad. Sci., 49, 96 (1959).
76. K. Ahmed and N. V. Subba Rao, Proc. Indian Acad. Sci., 55, 185, 284 (1962); 64, 141 (1966); 73, 250 (1971).
77. N. V. Subba Rao and V. V. Somayajulu, Proc. Indian Acad. Sci., 59, 396 (1964).
78. N. V. Subba Rao and V. V. Somayajulu, Proc. Indian Acad. Sci., 61, 139 (1965).
79. N. V. Subba Rao and V. V. Somayajulu, Proc. Indian Acad. Sci., 61, 177 (1965).
80. N. V. Subba Rao and K. S. R. K. Mohan Rao, Indian J. Chem., 3, 522 (1965).

81. N. V. Subba Rao, K. S. R. K. Mohan Rao, and S. Subhadra Kumari, Proc. Indian Acad. Sci., 69, 88 (1969).
82. N. V. Subba Rao and K. S. R. K. Mohan Rao, Indian J. Chem., 6, 66 (1968).
83. N. V. Subba Rao, K. S. R. K. Mohan Rao, and A. Krishnamurty, J. Indian Chem., 49, 1025 (1972); 50, 213 (1973).
84. N. V. Subba Rao, K. S. R. K. Mohan Rao, and A. Krishnamurty, 10, 38 (1972).
85. N. V. Subba Rao, K. S. R. K. Mohan Rao, and A. Krishnamurty, Indian J. Appl. Chem., 35, 90 (1972).
86. N. V. Subba Rao, K. S. R. K. Mohan Rao, and S. Subhadra Kumari, Proc. Indian Acad. Sci., 77, 149 (1973).
87. N. V. Subba Rao, K. S. R. K. Mohan Rao, and S. Subhadra Kumari, Indian J. Chem., 11, 541 (1973).
88. N. V. Subba Rao, K. S. R. K. Mohan Rao, and S. Subhadra Kumari, Symposium — Golden Jubilee Convention of the Indian Chem. Soc., Calcutta (1973).
89. N. V. Subba Rao, K. S. R. K. Mohan Rao, and E. V. S. Bhushan Rao, Curr. Sci., 42, 498 (1973).
90. N. V. Subba Rao, K. S. R. Mohan Rao, and Y. Uma Devi, Curr. Sci., 41, 773 (1972).
91. N. V. Subba Rao, K. S. R. K. Mohan Rao, and A. Krishnamurty, Austral. J. Chem., 21, 2315 (1968).
92. K. S. R. K. Mohan Rao and P. L. K. M. Rao, Proc. Indian Acad. Sci., 81, 262 (1975).
93. K. S. R. K. Mohan Rao, A. Krishnamurty, and N. V. S. Subba Rao, Indian J. Chem., 11, 1074 (1973).
94. K. S. R. K. Mohan Rao, M. C. Ganorkar, and B. Bharat Kumar, Golden Jubilee Convention of of the Indian Chem. Soc., Calcutta (1973).
95. K. S. R. K. Mohan Rao, M. C. Ganorkar, and N. R. C. S. I. R. Narasimha Rao, Convention at Roorkee (1975).
96. V. R. Srinivasan and G. Ramachander, J. Sci. Indian Res., 20C, 351 (1961).
97. G. Ramchander and V. R. Srinivasan, J. Sci. Indian Res., 21C, 44 (1962).
98. G. Ramchander and V. R. Srinivasan, J. Sci. Indian Res., 21C, 70 (1962).
99. G. Ramchander and V. R. Srinivasan, Medicina Experimentalis, 6, 288 (1962).
100. V. R. Srinivasan and G. Ramchander, Indian J. Chem., 1, 234 (1963).
101. G. Ramchander and V. R. Srinivasan, Curr. Sci., 28, 368 (1959).
102. V. R. Srinivasan, G. Ramchander, and Naqui Syeda, Arch. Pharm., 295, 405 (1962).
103. Husain Syeda, V. R. Srinivasan, and T. G. S. Nath, Indian J. Chem., 9, 642 (1971).
104. Naqui Syeda and V. R. Srinivasan, J. Sci. Indian Res., 21B, 196 (1962).
105. K. S. R. K. Mohan Rao, T. G. S. Nath, and V. R. Srinivasan, Austral. J. Chem., 28, 2089 (1975).
106. K. S. R. K. Mohan Rao, T. G. S. Nath, and V. R. Srinivasan, Indian J. Chem. (in press).
107. D. S. Seshpande, T. G. S. Nath, and V. R. Srinivasan, Indian J. Chem., 13, 851 (1975).
108. Naqui Syeda and V. R. Srinivasan, Tetrahedron Lett., No. 25, 1193 (1962).
109. Naqui Syeda and V. R. Srinivasan, Indian J. Chem., 3, 162 (1965).
110. V. Ranga Rao and V. R. Srinivasan, Indian J. Chem., 8, 509 (1970).
111. V. Ranga Rao and V. R. Srinivasan, Indian J. Chem., 3, 417 (1965).
112. V. Ranga Rao and V. R. Srinivasan, Experientia, 20, 200 (1964).
113. V. Ranga Rao and V. R. Srinivasan, in: Proceedings of the Symposium of Heterocyclic Compounds of Physiological INterest, Hyderabad (1964), p. 137.
114. T. Radha Vakula, V. Ranga Rao, and V. R. Srinivasan, Curr. Sci., 35, 487 (1966).
115. T. Radha Vakula, V. Ranga Rao, and V. R. Srinivasan, Indian J. Chem., 7, 577 (1969).
116. T. V. Saraswathi, V. Ranga Rao, V. R. Srinivasan, and M. Ramaiah, Indian J. Chem., 10, 1151 (1972).
117. T. Radha Vakula, T. V. Saraswathi, and V. R. Srinivasan, Indian J. Chem., 6, 172 (1968).
118. T. Radha Vakula and V. R. Srinivasan, Indian J. Chem., 7, 580 (1969).
119. T. Radha Vakula and V. R. Srinivasan, Indian J. Chem., 7, 583 (1969).
120. T. Radha Vakula and V. R. Srinivasan, Indian J. Chem., 7, 760 (1969); 732 (1973).
121. T. Radha Madhavan and V. R. Srinivasan, Indian J. Chem., 9, 901 (1971).
122. T. Radha Vakula, V. Ranga Rao, and V. R. Srinivasan J. Prakt. Chem., 315, 185 (1973).
123. T. V. Saraswathi and V. R. Srinivasan, J. Sci. Indian Res., 30, 54 (1971).
124. T. V. Saraswathi and V. R. Srinivasan, Tetrah. Lett. N 25, 2316 (1971).
125. T. V. Saraswathi and V. R. Srinivasan, Symposium in Organic Chemistry, University of Madras (1973), Abstract No. 34 p. 32.
126. D. S. Desphande and V. R. Srinivasan, Sixth International Symposium on Organic Sulphur Chemistry, Bangor, Wales, England (1974), Abstract No. D. 22.