SUMMARY

1. The methods of preparation of $\alpha$-functionalized thionoacetic acid derivatives and $\alpha$-functionalized ketene thioacetals, and their application in the synthesis of heterocycles have been reviewed.

2. The chemistry of mononuclear isothiazoles has been reviewed with special emphasis on the synthetic routes involving cyclization methods.

3. The hitherto inaccessible 3,5-diaminoisothiazoles have been synthesized by the cyclization of 3-amino-3-mercaptoacrylonitrile salts with chloramine. A variety of 3-aminoisothiazoles with an alkylamino, dialkylamino, arylamino and arylsulfonylamino substituent at the 5-position have been prepared by this method. The 3-amino-3-mercaptoacrylonitrile salts were generated through the base promoted condensation of isothiocyanates with active methylene nitriles and through the reaction of $\alpha$-cyanoketene S,N-acetals with sodium sulfide.

4. 3-Aminoisothiazoles with an alkoxy, aryloxy, alkylthio and arylthio substituent at the 5-position have been prepared by the cyclization of appropriate $\alpha$-cyanothionoacetic acid intermediates with chloramine. 3-Amino-4-
carbethoxyisothiazole-5-sulfenamide and 3,4-diaminoisothiazolo(4,5-d)isothiazole have been obtained as the product of reaction of chloramine with the dithiolates derived from the reaction of carbon disulfide with ethyl cyanoacetate and malononitrile, respectively.

5. Analogous to the cyclization of 3-mercaptoacrylonitrile intermediates to 3-aminoisothiazoles, the cyclization of the phenyl isothiocyanate adducts of \( \alpha \)-methylene ketones and enamines, with chloramine, has been found to yield the corresponding 3-alkyl- and 3-aryl-5-(phenylamino)isothiazole derivatives. 3-Amino-5-(phenylamino)-1,2,4-thiadiazole has been obtained by the cyclization of the phenyl isothiocyanate adduct of cyanamide with chloramine.

6. The effectiveness of other oxidizing agent-ammonia combinations, in place of chloramine, for the cyclization of certain 3-mercaptoacrylonitrile derivatives has been studied.

7. 3-Hydroxy-4-cyano-5-(arylamino)isothiazoles have been obtained as the major products of reaction of 3-mercapto-3-(arylamino)-2-cyanoacrylamide salts with chloramine. They have also been isolated as by-products in the cyclization of 3-mercapto-3(arylamino)-2-carbethoxyacrylonitriles to
3-amino-4-carbethoxy-5-(arylamino)isothiazoles.

8. The isothiazoles synthesized have been found to undergo the normal reactions expected of the amino group at the 3-position and of the cyano, ester and amide function at the 4-position. The 3-amino-4-cyano-5-(methylsulfonyl) isothiazole, prepared by the oxidation of 3-amino-4-cyano-5-(methylthio)isothiazole, has been found to undergo facile nucleophilic displacement reaction with methylamine to yield the 3-amino-4-cyano-5-(methylamino)isothiazole. The 3-amino-4-carbethoxy-5-(phenylamino)isothiazole has been found to yield 2-(cyanocarbethoxymethylene)benzothiazoline as the product of reaction with nitrous acid. A probable mechanism for this ring transformation has been proposed.

9. Isothiazolo(3,4-d)pyrimidines have been synthesized by the cyclization of 3-aminoisothiazoles possessing a nitrile, ester or amide function at the 4-position.

10. The physical and spectroscopic properties of the isothiazoles and isothiazolopyrimidines have been studied.

11. The amine-imine tautomerism in the 3,5-diaminoisothiazoles has been studied. The UV, IR, and NMR spectral characteristics indicate that the potentially tautomizerable 3,5-diaminoisothiazoles, in general, exist predominantly
in the diamine form.

12. The mass spectral fragmentation pattern of the aminoisothiazoles and isothiazolopyrimidines has been studied. An attempt has been made to assign, tentatively, the structure of some of the most abundant fragment ions found in the spectra of these compounds.

13. A few of the aminoisothiazoles and isothiazolopyrimidines have been screened for analgesic and antiinflammatory activities as well as for antimicrobial activity against Gram-positive and Gram-negative bacteria. Some of the 3-amino- and 3,5-diaminoisothiazoles have been screened for antimalarial and antitrypanosomal activities.

14. The synthesis of 3-unsubstituted-, 3-alkyl-, 3-aryl-, 3-hydroxy- and 3-aminothiophenes by the intramolecular cyclization of open-chain thioether intermediates through $C_2$-$C_3$ bond forming reactions, has been reviewed.

15. $\alpha$-Cyanoketene $S,S$- and $S,N$-acetals have been found to react with ethyl thioglycolate to yield 3-amino-2-carbethoxy-4,5-disubstituted thiophene derivatives. 3-Hydroxy-4-cyano-2-carbethoxy-5-substituted thiophenes have been isolated from the reaction of certain $\alpha$-cyano-$\alpha$-carbethoxyketene thioacetals.
16. The alkylative cyclization of 3-substituted-3-mercaptoacrylonitrile salts to thiophenes has been studied. While the reaction of the salts of 3-mercapto-3-(N-monosubstituted)aminoacrylonitriles with ethyl chloroacetate \( \alpha \)-bromoacetylacetone, ethyl bromocyanooacetate and phenacyl bromide has been found to yield the 2-(\( \alpha \)-substituted methylene) thiazoline and thiazolidine derivatives, their reaction with ethyl \( \alpha \)-chloroacetoacetate, ethyl \( \alpha \)-bromoacetoacetate or diethyl bromomalonate yields 2-carbethoxy-3-aminothiophene derivatives as the major products of the reaction.

17. Some 2-(2-benzimidazolyl)-3-amino-4,5-disubstituted thiophenes have been prepared by a facile reaction involving the alkylative cyclization of 2,3-disubstituted-3-mercaptoacrylonitriles with the readily available 2-chloromethylbenzimidazole.

18. The condensation of 2-chloromethylbenzimidazole with enamine-isothiocyanate adducts and \( N \)-acyl thioureas has led to the formation of the corresponding substituted 2-(2-thienyl)- and 2-(5-thiazolyl)benzimidazoles.

19. Thieno(3,4-d)pyrimidines and thieno(3,2-d)-
pyrimidines have been synthesized by the cyclization of the 3-aminothiophene derivatives possessing an ester, amide or nitrile function at the 2- or 4-position.

20. Benzimidazo(1,2-c)thieno(2,3-e)pyrimidines have been prepared by the cyclization of 3-amino-2-(2-benzimidazolyl)thiophenes with ortho esters and acid chlorides. Benzimidazo(1,2-c)thieno(2,3-e)triazines have been obtained by the reaction of 3-amino-2-(2-benzimidazolyl)thiophenes with nitrous acid.

21. The physical and spectroscopic properties of the 3-aminothiophenenes, thienopyrimidines and condensed thiophenes have been studied.

22. Some of the 3-aminothiophenenes and their derivatives have been screened for analgesic and antiinflammatory activities.

23. A brief account of the reactions of nitriles that are conducted under the influence of halogen acids is given. The use of nitriles in the synthesis of quinazolines by reaction with o-aminocarbonyl compounds has been summarized.
24. The reaction of nitriles with o-aminocarbonyl compounds such as an o-aminoester, o-aminoamide, o-aminonitrile and o-aminoketone, under acidic conditions, has been studied. Aliphatic, aromatic and heterocyclic nitriles have been found to undergo facile condensation with o-aminocarbonyl derivatives of benzene, thiophene, pyrrole and isothiazole, in the presence of hydrogen chloride, to afford the corresponding condensed pyrimidine derivatives. The hydrogen chloride catalysed condensation of a nitrile with an o-aminosulfonamide has yielded the corresponding 1,2,4-benzothiadiazine 1,1-dioxide.

25. The applicability of other acid catalysts in place of hydrogen chloride as well as the effectiveness of base catalysis in the condensation of nitriles with certain o-aminocarbonyl compounds has been studied. The generality, scope and limitation of the halogen acid catalysed condensation of o-aminocarbonyl compounds with nitriles to obtain condensed pyrimidines has been discussed.

26. The physical and spectroscopic properties of the condensed pyrimidines have been studied.