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Methods of Synthesis of Imidazopyrimidines with a Bridgehead Nitrogen Atom and Their Benzo-analogues

I.A.Mazur, B.E.Mandrichenko, and R.I.Katkevich

The methods of synthesis of imidazopyrimidines with a bridgehead nitrogen atom, namely imidazo[1,2-*a*]pyrimidines, imidazo[1,2-*c*]pyrimidines, and their benzo-analogues, are examined, particular attention being devoted to methods of synthesis of preparative value. Certain theoretical problems associated with the formation of these heterocyclic condensed systems are discussed.
The bibliography includes 157 references.

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I. INTRODUCTION

Among the nitrogen-containing heterocycles which are constituents of alkaloids, vitamins, nucleic acids, enzyme systems, etc. imidazolines with a bridgehead nitrogen atom, namely imidazo[1,2-*a*]- and imidazo[1,2-*c*]-pyrimidines, have attracted attention in recent years. Derivatives of the latter type—the alkaloids alchornine, alchornidine, and alchorneine—have been recently isolated from plants of the genus *Alchornea*.[1-3]

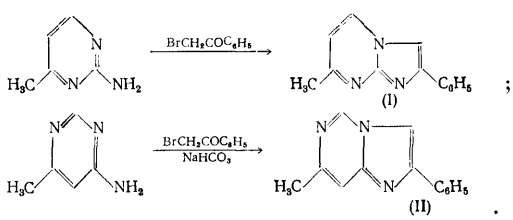
The search undertaken in recent years for biologically active imidazopyrimidines with a bridgehead nitrogen atom, which are structural analogues of purines, led to the detection among them of comoounds with a broad spectrum of biological activity[4-18]. This resulted in an increased interest in the development of procedures and methods for the synthesis of these heterocyclic sytems.

The present review is in essence the first attempt at a survey and a critical examination of the literature data, mainly those obtained recently, on the methods of synthesis of imidazopyrimidines with a bridgehead nitrogen atom, since the information on this problem quoted in Shvachkin's review[19], published 20 years ago, is extremely limited and already obsolete. In the present review, a systematic account is given of all the available literature data and the methods of synthesis of imidazo[1,2-*a*]- and imidazo[1,2-*c*]-pyrimidine systems and the limits of their applicability and preparative value are estimated.

II. ALKYLATION OF AMINOPYRIMIDINES AND AMINOIMIDAZOLES

1. Alkylation of 2(4)-aminopyrimidines

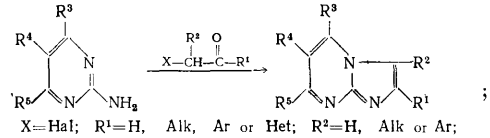
The classical method for the preparation of imidazo[1,2-*a*]- and imidazo[1,2-*c*]-pyrimidines, the alkylation of 2-amino- and 4-amino-pyrimidines, was achieved for the first time by Ochiai and Jamai[20] in 1939. By heating 2-amino-6-methyl- and 4-amino-6-methyl-pyrimidines with phenacyl bromide, they synthesised 7-methyl-2-phenylimidazo[1,2-*a*]-pyrimidine (I) and 7-methyl-2-phenylimidazo[1,2-*c*]-pyrimidine (II):



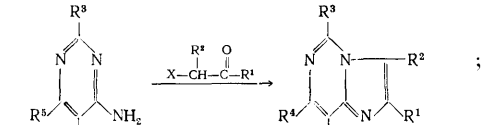
Subsequently, the method was applied to the synthesis of a whole series of unsubstituted and *C*- or *N*-substituted 2- and 4-aminopyridines[12-14,21-46]. The wide scope of this reaction, which is suitable for the synthesis of virtually all imidazopyrimidines with functional groups, is illustrated in Scheme 1.

The method discussed is fairly promising, since it permits the use of a whole series of alkylating agents and an appreciable variation of the experimental conditions. The alkylating agents employed were α-bromo(chloro)-ketones and α-bromo(chloro)aldehydes or their acetals. The alkylation process is usually carried out by heating equimolar amounts of the reactants to 60–100°C in an organic solvent (pure alcohols, dioxan, toluene and dimethylformamide) or in water. In order to prevent the formation of salts by the aminopyrimidines[46], which hinders the reaction, basic reagents are used: sodium hydroxide, sodium bicarbonate, and trialkylamines[31].

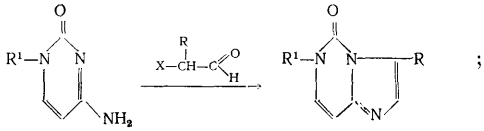
Scheme 1



X=Hal; R^1=H, Alk, Ar or Het; R^2=H, Alk or Ar; R^1R^2=$-(CH_2)_n-$; R^3=H, OH, Alk or Ar; R^4=H, OH, OAlk, Hal or NO_2; R^5=H or Alk; R^4R^5=$-(CH_2)_n-$.



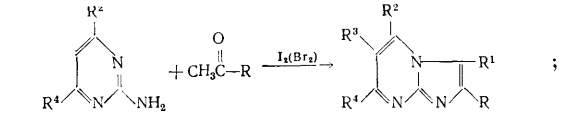
X=Hal; R^1=H, Alk, Ar or Het; R^2=H, Alk or Ar; R^3=H, Alk, OH or OAlk; R^4=H, OAlk or Hal; R^5=H or Hal.



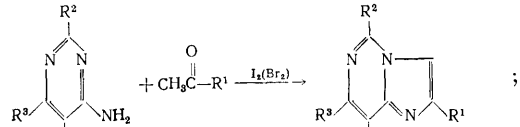
X=Cl or Br; R=H or Alk; R^1=Alk .

Apart from its advantages, the method suffers from a significant defect associated with the powerful lachrymatory action of α-halogenocarbonyl compounds. A version of the single-stage synthesis of imidazopyrimidine derivatives [47-49] (Scheme II), which excludes the stages involving the preparation and purification of the halogenocarbonyl component, is therefore of interest. A second undoubted advantage of this type of synthesis is the possibility of obtaining pure non-halogenated imidazopyrimidines and also their mono- and di-halogeno-derivatives, which is achieved by a strict control of the quantitative proportions of bromine and the other reagents.

Scheme 2

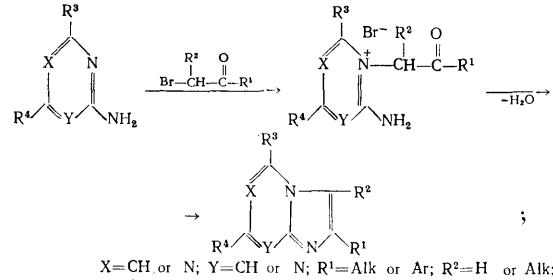


R=Alk or Ar; R^1=H or Br; R^2=H or OH; R^3=H or Br; R^4=H or Alk.



R^1=Alk or Ar; R^2=H or OAlk; R^3=OAlk or Cl; R^4=H or Br.

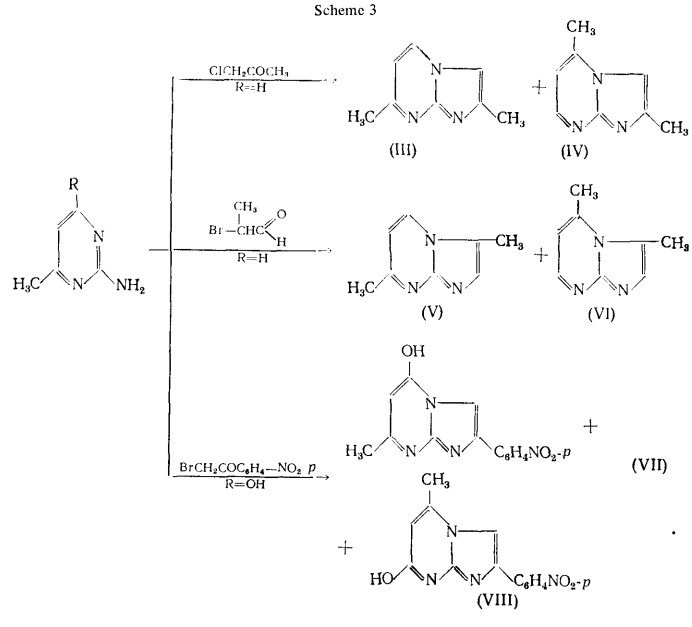
The interaction of aminopyrimidines with α-halogenoaldehydes (and α-halogenoketones) can proceed in theory via an initial stage involving the quaternisation of the pyrimidine nitrogen atom or via the formation of Schiff bases. Shvachkin [19] shares the view of Ochiai and Jamai [20], who believe that the initial step in this reaction is the formation of azomethines, which cyclise in the presence of bases. Recent studies [37,38,41-43,46] have shown that aminopyrimidines are quaternised, forming extremely labile salts, which are readily converted into imidazopyrimidines on heating or when an attempt is made to isolate the free bases. There is no doubt about the formation of the quaternary salts and it is convincingly supported by spectroscopic data:



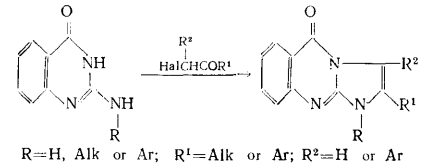
X=CH or N; Y=CH or N; R^1=Alk or Ar; R^2=H or Alk; R^3=H, OH or OAlk; R^4=H, Alk, OAlk or Hal.

The alkylation of asymmetric 2-aminopyrimidines [38,43,46] by α-halogeno ketones and α-halogenoaldehydes can involve the $N_{(1)}$ and $N_{(3)}$ atoms, which leads to an isomeric mixture of products (III) and (IV), (V) and (VI), and (VII) and (VIII) respectively. Determination of the isomeric composition of the reaction products showed that compounds (III), (V), and (VII) predominate, which can probably be accounted for by steric factors (Scheme 3).

Scheme 3



The alkylation method proved to be suitable for the synthesis of 1,5-dihydroimidazo[2,1-*b*]-5-quinazolone derivatives from 2-amino(alkyl or aryl-amino)-4-quinazolones and α-halogenoketones [49,50]:

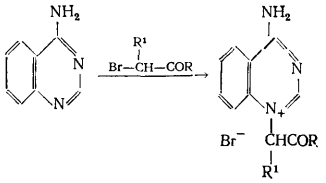


R=H, Alk or Ar; R^1=Alk or Ar; R^2=H or Ar

It is remarkable that, in contrast to the majority of α-amino-substituted nitrogen-containing heterocycles, which are alkylated at the endocyclic nitrogen atom adjoining the amino-group, 4-aminoquinazoline interacts with α-halogenoketones preferentially with formation of

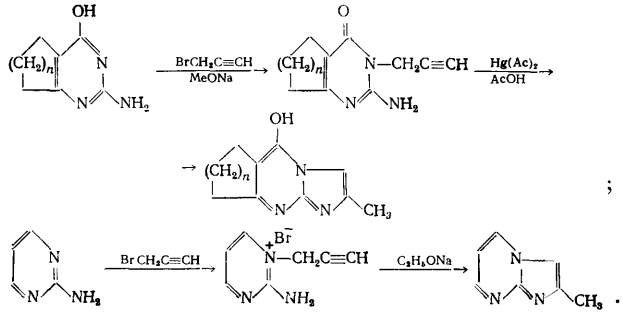
1-acylalkyl-4-aminoquinazolinium quaternary salts [49,51]. The attack by the alkylating agent on the $N_{(1)}$ atom can be explained on the basis of the molecular diagrams in Armarego's monograph [52].

The specificity of the alkylation of 4-aminoquinazolines by α-halogenoketones precluded the synthesis of imidazo-[1,2-*c*]quinazoline derivatives by this method [49,51]:



R=Alk, Ar or Het; R¹=H or Alk

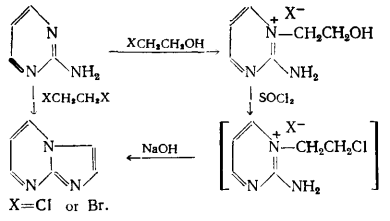
Together with α-halogenocarbonyl compounds, propargyl bromide can be used as the alkylating agent to obtain 2-methyl-substituted imidazopyrimidines [14,54,54]:



It follows from the above scheme that *N*-propargyl derivatives can be converted into methylated imidazo-pyrimidines in two different ways: by the Kucherov hydration of the triple bond with subsequent cyclisation of via the nucleophilic amination of the triple bond under the conditions of base catalysis.

β-Halogenoalcohols and 1,2-dihalogenoalkanes [46,49,55-57], which alkylate 2-amino-, 2-arylamino-, and 4-amino-pyrimidines and 2-amino(alkyl- or arylamino)-4-quin-azolones, have been used to synthesise hydrogenated analogues of imidazopyrimidines (quinazolines). [49,57]

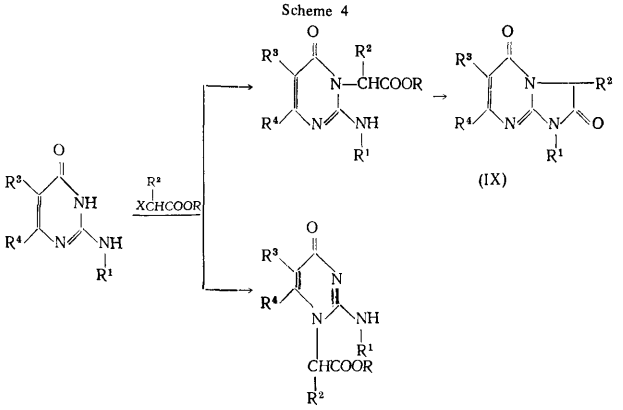
In practice it is better to use dihalogenoalkanes in this reaction, since the latter can then be carried out in one stage [46,56,57]:



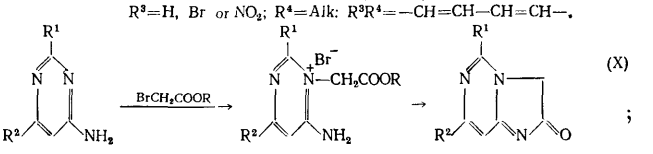
X=Cl or Br.

The use of α-halogenocarboxylic acids and their esters makes it possible to obtain a series of different 2-oxo-derivatives of imidazopyrimidine (quinazoline) from 2-amino- and 4-aminopyrimidines [46,49,58-60] and 2-amino-(alkyl- or arylamino)-4-quinazolinones [49] (Scheme 4).

Scheme 4



X=Cl, Br or I; R=H or Alk; R¹=H, Alk or Ar; R²=H or Alk; R³=H, Br or NO_2; R⁴=Alk; R³R⁴=—CH=CH—CH=CH—.



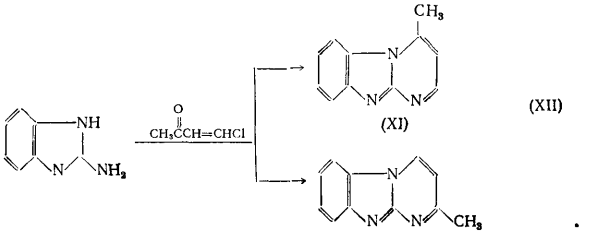
R=Alk; R¹=H or OAlk; R²=Cl or OAlk

It should be noted particularly that alkylation of asymmetric 2-aminopyrimidines by α-halogenocarboxylic acids (or esters) involves simultaneously the $N_{(1)}$ and $N_{(3)}$ atoms [46,49,58]. The intermediate *N*-carboxyalkyl-(alkoxycarbonylalkyl)pyrimidines (quinazolines) are extremely labile and frequently cyclise under reaction conditions to hydrogenated 2-oxo-derivatives of imidazo-pyrimidine (quinazoline). [46,49,58-60] The presence of active centres in compounds (IX) and (X) makes them important intermediates in the syntheses of potential biologically active substances or dyes [46,49,59,60].

The use of the anhydrides of α-halogenocarboxylic acids in the reaction leads to the initial formation of *N*-acyl derivatives of 2-aminopyrimidines, which cyclise under conditions which are relatively unsuitable for practical purposes and with fairly low yields [19,61-69].

2. Alkylation of 2-Aminoimidazoles

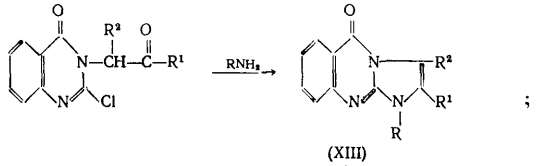
Imidazopyrimidines with a bridgehead nitrogen atom can be synthesised by alkylating 2-aminoimidazoles. On treatment with β-chlorovinyl methyl ketone, 2-amino-benzimidazole is known to be converted [70] into 4-methyl-pyrimido[1,2-*a*]benzimidazole (XI) and 2-methylpyrimido-[1,2-*a*]benzimidazole (XII) in proportions of 8 : 1.



Kochergin [71] demonstrated the possibility of obtaining tetrahydropyrimido[1,2-*a*]benzimidazole from 1-alkyl-2-aminobenzimidazole and 1,3-dihalogenopropane.

III. AMINATION OF HALOGENO-, ALKYLTHIO-, AND ARYLOXY(ALKOXY)-DERIVATIVES OF PYRIMIDINE AND IMIDAZOLE

The amination of halogeno-, alkylthio-, and aryloxy-(alkoxy) derivatives of pyrimidine (quinazoline) and imidazole constitutes a method of preparation of imidazopyrimidines and their benzo-analogues which is no less important on a preparative scale. In most cases, this method is more laborious than the previous one, but it has nevertheless found applications in the synthesis of imidazopyrimidine systems and their hydrogenated analogues. The nucleophilic substitution of the halogeno-, alkylthio-, and aryloxy(alkoxy)-groups in the above systems is usually carried out in organic solvents over a wide temperature range. Armarego[72] and other workers[73,74] modified the general method somewhat. They synthesised imidazo[1,2-*a*]- and imidazo[1,2-*c*]pyrimidines from 2-chloro- and 4-chloro-pyrimidines and aminoacetals[72-74] in the presence of potassium iodide. The conversion of the initial chloropyrimidines into the more reactive iodopyrimidines made it possible to achieve quantitative yields of α-pyrimidinylaminoacetals. Depending on the type of cyclising agents, the latter are converted into the corresponding imidazo-, 3-hydroxyimidazolino-, and 3-alkoxyimidazolino-pyrimidines (Scheme 5). The reaction with 4-chloroquinazoline proceeds similarly[4].



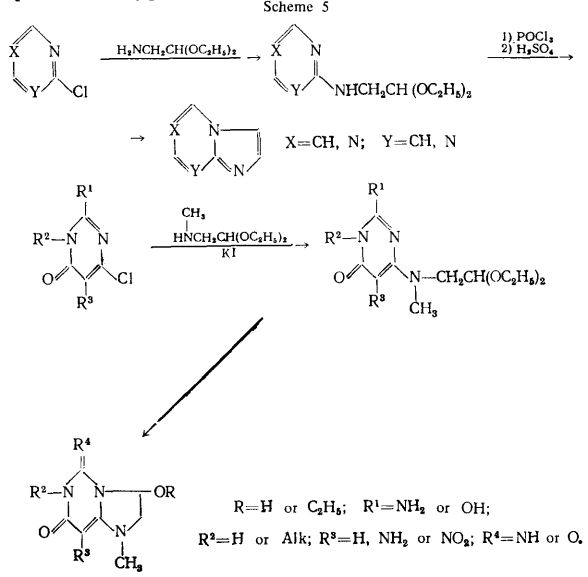
(XIII)

R=H, Alk or Ar; R^1=Alk, or Ar; R^2=H or Ar.

Pfleiderer et al,[74] who aminated 4-chloro-5-nitropyrimidine-2,6-diones with glucosamine in an aqueous alkaline medium, demonstrated the possibility, in principle, of obtaining 2-formyl-3-hydroxy-8-nitro-1,2,3,5,6,7-hexahydroimidazo[1,2-*c*]pyrimidine-5,7-dione and its 6-substituted derivatives.

An interesting method for the synthesis of imidazoquinazolin-5-ones has been proposed recently[49,75]: 3-acylalkyl-2-chloroquinazolin-4-ones are aminated with ammonia and primary amines[76] and are readily converted into compounds of type (XIII)

Scheme 5



X=CH, N; Y=CH, N

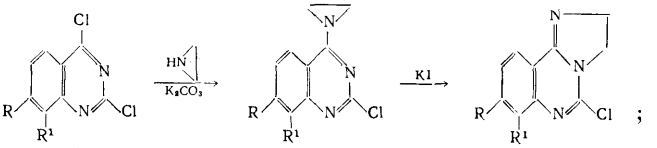
R=H or C_2H_5; R^1=NH_2 or OH; R^2=H or Alk; R^3=H, NH_2 or NO_2; R^4=NH or O.

There have been a number of communications[4,72,79-82,87,126,140-146] in which the results of studies of the interaction of chloro- and alkylthio-pyrimidines (quinazolines, purines) with aminoalcohols and their ethers are presented. In this case, the hydrogenated imidazopyrimidine systems are synthesised in two stages involving the formation of β-hydroxyalkylaminopyrimidines with their subsequent conversion into the corresponding cyclising β-chloro-derivatives. For this reason, it is better to use β-halogenoalkylamines instead of β-aminoalcohols in this reaction[77,79-86].

Hornyak and Lempert[87] replaced the stage involving the halogenation of the intermediate heterylaminoalcohols by their oxidation with chromium trioxide in acetic acid or anhydride. It is remarkable that the use of this procedure leads to the formation of 3-hydroxyimidazopyrimidines.

Reiter and coworkers[88,89] developed a method for the thermal cyclisation of β-aryloxyethylaminopyrimidines, which greatly simplified the preparation of imidazopyrimidines.

The method of synthesis of imidazolinoquinazolines, using aziridine as the aminating agent, is of some interest. According to patent data[11], the initial 2,4-dichloroquinazolines are selectively aminated in the 4-position under fairly mild conditions. Subsequent treatment of the aminated product with potassium iodide in acetone leads to the formation of a tricyclic product:

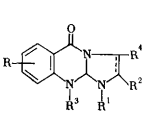


R=R^1=H or OCH_3.

The amination of 4-chloroquinazoline with ethylenediamine results in the formation of imidazolino[1,2-*c*]-quinazoline[90], but the ambiguity of the reaction pathway lowers sharply the advantage of this method.

Hydrogenated imidazo[1,1-*b*]quinazoline and pyrimido[1,2-*f*]xanthine systems have been obtained by treating 2-chloro-3-(β-chloroethyl)quinazolin-4-one[91-93] and 8-bromo-7-(γ-bromopropyl)theophylline[94] with ammonia, primary amines and hydroxylamine. The scope of this method is limited owing to the low availability of the labile halogeno-components.

A number of publications have appeared in recent years indicating the possibility of using alkylthio-derivatives of imidazoles and benzimidazoles for the synthesis of imidazopyrimidine systems. 2-Alkylthioimidazolines and their *N*-substituted derivatives[95-99] as well as 2-alkylthiobenzimidazoles[100,101] give rise to tri- and tetra-cyclic products on heating with *o*-aminobenzoic acids, their anhydrides, isatin, or isatoic acids:

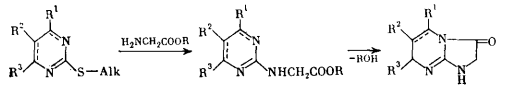


R=H, OH, OAlk, Hal, Het, SO_2Cl or SO_2NH_2; R^1=H or Alk; R^1R^2=$-(CH_2)_4-$; R^3=H, Alk or Ar; R^3R^4=$-CH=CH-CH=CH-$; ═══ single or double bond.

Similar compounds may be obtained from 2-halogenoimidazoles[100-105].

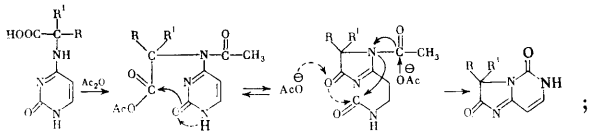
There exist two radical approaches to the solution of the problem of synthesising hydrogenated imidazopyrimidin-2(3)-ones. One of these involves the amination of halogeno- or alkylthio-pyrimidines by aminoacids or their esters. This method has been used successfully to synthesise hexahydroimidazo[1,2-*a*]pyrimidin-3-one[106-107], tetrahydroimidazo[1,2-*c*]pyrimidin-2-ones[69], tetrahydroimidazo[2,1-*a*]quinazolin-3-ones[108,109], dihydroimidazo[1,2-*c*]quinazolin-2-ones[49], and dihydroimidazo-[1,2-*i*]purin-2-ones[110-112].

The reaction of 2(4)-halogeno- or alkylthio-pyrimidines (quinazolines) with aminoacids or their esters, which is distinguished by its simplicity, proceeds with high yields on heating (as a rule in lower alcohols) to 20–100°C:



R=H or Alk; $R^1=R^2=2H$; $R^1R^2=-CH=CH-CH=CH-$; R^3=H or OH; ═══ single or double bond.

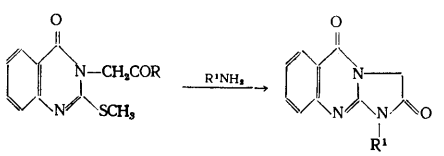
Tetrahydropyrimidin-2-ylaminoacetic acid and its esters obtained in this way[106,107] are unstable in the form of the hydrochlorides; their neutralisation leads to the formation of hexahydroimidazo[1,2-*a*]pyrimidin-3-one. In contrast to these, *N*-(4-oxoquinazolin-2-yl)aminoacetic acid is entirely stable and its cyclisation in the presence of dicyclohexylcarbodiimide or acetic anhydride proceeds preferentially along the "*a*" edge of the quinazoline ring with formation of cyclic 3-oxo-derivatives[108,109]. The reactions of *N*-(pyrimidin-4-yl, quinazolinyl, and adenin-6-yl)-α-aminocarboxylic acids under the conditions of cyclisation by glacial acetic acid or the acetic acid–acetic anhydride mixture have been described[49,69,110-112]. The thorough investigation by Ueda and Fox[69], where two alternative pathways to the cyclisation of *N*-(2-oxopyrimidin-4-yl)-α-aminocarboxylic acids were considered, is noteworthy. The authors showed that the only reaction products are 3-alkyl-1,2,3,5-tetrahydroimidazo-[1,2-*c*]pyrimidine-2,5-diones and proposed the following mechanism for their formation:



R=R¹=H or Alk.

Similar results were obtained in the cyclisation of *N*-(quinazolin-4-yl, adenin-6-yl)-α-aminocarboxylic acids[49,110-112]. Using a tracer atom method, Chheda and coworkers[110,111] finally confirmed in recent years the validity of Ueda's theoretical postulates.

Another version involves the use of the esters or amides of 2-methylthioquinazolin-3-ylacetic acid[91,108,109,113-116]:



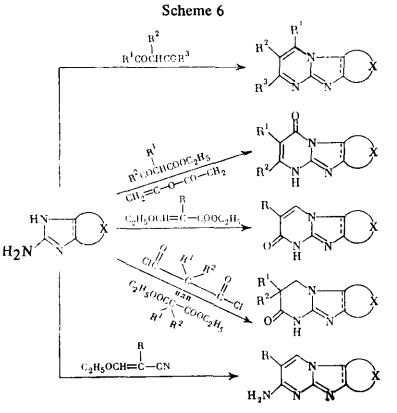
R=OAlk or NH_2; R^1=H, Alk or Ar.

Unfortunately, this method, which is synthetically more promising since it does not require the use of aminoacids or their esters, has not been extended to other systems.

IV. CONDENSATION OF 2-SUBSTITUTED IMIDAZOLES WITH ALDEHYDES, 1,3-DICARBONYL COMPOUNDS, ACIDS, AND THEIR DERIVATIVES

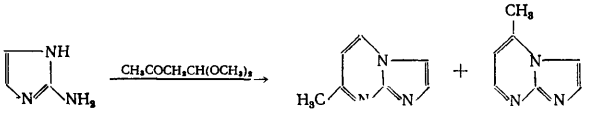
Condensation as a method of synthesis of imidazopyrimidine systems has been known for a long time. Using 2-aminoimidazoline and acetoacetic ester, Kawai[117] obtained for the first time in 1931 7-methyltetrahydroimidazo[1,2-*a*]pyrimidine. Subsequently the preparative possibilities of this method were widely investigated by many workers. The extensive study of this reaction was favoured by the relative availability of the initial 1,3-dicarbonyl compounds and 2-aminoimidazoles (benzimidazoles) and their hydrogenated analogues. This type of condensation (Scheme 6) is convenient for the synthesis of polynuclear heterocyclic systems with an imidazopyrimidine fragment. At the same time, one should note the ambiguity of this reaction, which leads to the formation of a mixture of isomeric products. Despite the difficulty of separating the isomers, this method can be regarded as sufficiently preparative, permitting the variation of the experimental conditions (temperature, reaction time, solvent, and pH of the medium).

Scheme 6

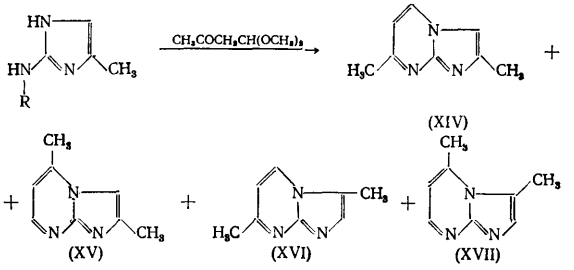


Here ═══ is a single or double bond and X are different substituents in the imidazole ring or the condensed benzene ring.

Imidazo[1,2-*a*]pyrimidine systems have been obtained by the condensation of 2-aminoimidazoles[30,34,38,118,119], 2-aminoimidazolines[117,120-125], and 2-aminobenzimidazoles[118,119,126-139] with 1,3-dicarbonyl compounds or substances which can be converted into these reagents under the reaction conditions. The 1,3-dicarbonyl compounds used were dialdehydes and their acetals, formylketones, diketones, ketoacids or their esters, diketens, dicarboxylic acids or their esters, and acid halides, as well as α,β-unsaturated acids, their chlorides, and esters. The composition of reaction products is determined by the structural characteristics of the reactants. Two isomeric products are usually obtained when 2-aminoimidazole or its 4,5-disubstituted derivatives with identical substituents are treated with asymmetric 1,3-dicarbonyl compounds[38,118,119,132,139]:



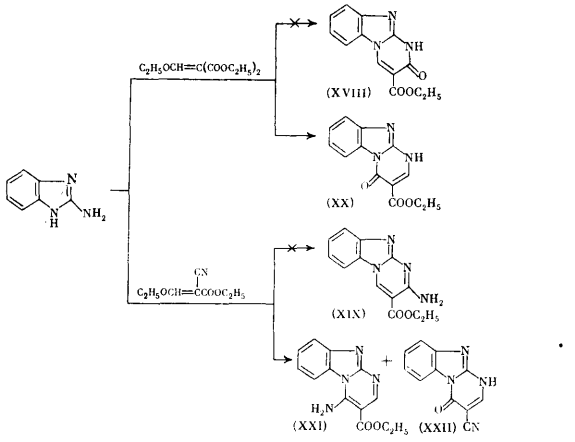
The condensation of 2-amino-4(5)-methylimidazole with the acetal of acetoacetaldehyde in a neutral medium leads to a four-component mixture of isomers (XIV)–(XVII), while in an acid medium a two-component mixture of compounds (XV) and (XVII) is obtained [38]:



(XIV) (XV) (XVI) (XVII)

The study of Chow et al. [139], who investigated the reaction of 2-aminobenzimidazole with bifunctional carboxylic acid derivatives, merits special attention, as they obtained results conflicting with earlier conclusions [119]. De Cat and von Dormael [119] claim that the condensation of 2-aminobenzimidazole with diethyl ethoxymethylenemalonate leads to compound (XVIII) and the reaction with ethyl cyanoethoxymethyleneacetate gives rise to compound (XIX).

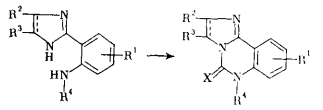
Chow et al. [139] reproduced these reactions under identical conditions and obtained, instead of compound (XVIII), its isomer (XX) and, instead of compound (XIX), the products were compounds (XXI) and (XXII):



(XVIII) (XX) (XIX) (XXI) (XXII)

In order to solve the structural problems, Chow et al. [139] carried out a series of chemical transformations of compounds (XX)–(XXII) and analysed their ^{1}H NMR spectra. In view of all these considerations, their data are fairly convincing, in contrast to earlier investigations, whose conclusions are doubtful and require additional tests.

Imidazo[1,2-*c*]quinazolines, which are of biological value [4-10,17,18], become available as a result of the condensation of imidazole-containing compounds, which serve as the diamino-components, with aldehydes [7,8,10], carboxylic acids, their chlorides, and thioanhydrides [5,8,10,15,147-150]:



X=O or S; R^1=Alk or Hal; R^2=R^3=H or Alk;
R^2R^3=—CH=CH—CH=CH—; R^4=H or Alk; ═══ single or double bond.

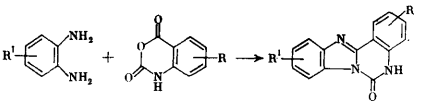
The study of Franchetti and Grifantini [151], who reduced 2-(*o*-nitrophenyl)-1-hydroxyimidazole 3-oxide with zinc to a tricyclic 5,6-dihydroimidazoquinazoline derivative, is of some interest.

Methods of synthesis of hexahydroimidazoquinazolines based on ethylenediamines and 1-acylaminobenzophenones have been patented [6,9].

The preparation of tetrahydroimidazo[1,2-*c*]quinazolines together with diazepines [152] or a mixture of imidazo[1,2-*c*]- and imidazo[2,1-*b*]-quinazolines [92] has been claimed.

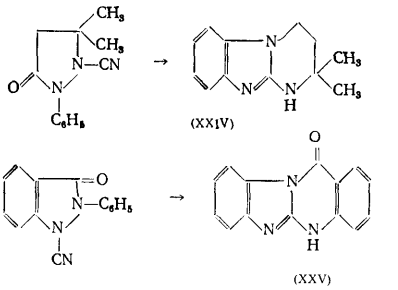
V. OTHER METHODS OF SYNTHESIS

Apart from the general methods discussed above, there are specific procedures for the synthesis of imidazopyrimidines and their benzo-analogues, which are important in particular instances and which have not found extensive use. Thus compounds of type (XXIII) are formed when *o*-phenylenediamine is fused with isatoic acids [148,153]:



R=H or CH_3; R^1=H, CH_3 or Cl (XXIII)

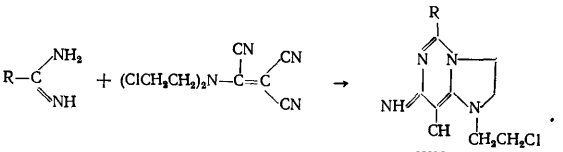
The reaction of ethylenediamine with 2,6-dithiobenzothiazine—the thio-analogue of isatoic acid—proceeds similarly [154]. A novel method has been described for the synthesis of benzimidazopyrimidines (XXIV) and (XXV) by heating 2-cyano-1-phenyl-3,3-dimethylpyrazolidin-5-one and 1-cyano-2-phenylbenzopyrazolidin-3-one at 270°C [155]:



(XXIV) (XXV)

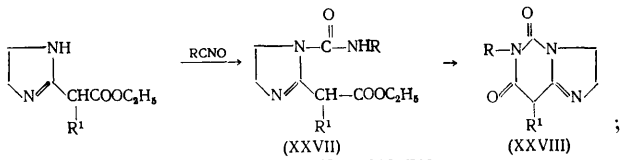
The authors do not discuss the mechanism of the formation of the above compounds.

1-β-chloroethyl-5-R-8-cyano-7-imino-1,2,3,7-tetrahydroimidazo[1,2-*c*]pyrimidines (XXVI) have been synthesised from amidines under the influence of bis-(β-chloroethylamine)tricyanoethylene [156]:



(XXVI)

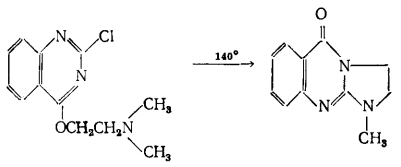
The use of cyanates in the reaction with ethyl imidazoline-2-acetates in benzene made it possible to obtain derivatives of hexahydroimidazo[1,2-*c*]pyrimidine-5,7-dione (XXVIII).[157] This process proceeds via a stage involving the formation of the intermediate (XXVII), which is converted into compound (XXVIII) on boiling in alcohol:



(XXVII) (XXVIII)

R=H or C_6H_5; R^1=H or C_6H_5NHCO.

It has been observed[92] that heating compound (XXIX) to 140°C for a short time results in the formation of traces of 1-methyltetrahydroimidazo[2,1-*b*]quinazolin-5-one:



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