Russian Chemical Reviews **66** (3) 187 – 204 (1997) © 1997 Russian Academy of Sciences and Turpion Ltd

UDC 547.78 + 547.86

Imidazo[1,2-*a*]pyrazines

V A Basiuk

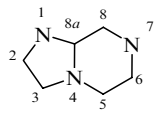
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Abstract. Published data on the methods for synthesis, reactions and natural occurrence of imidazo[1,2-*a*]pyrazines are surveyed. **Some other properties and applications of these compounds are also considered. The bibliography includes 273 references.**

I. Introduction

The class of imidazo[1,2-*a*]pyrazines (subsequently referred to as imidazopyrazines) comprises heterocyclic compounds based on a fused bicyclic system with a bridgehead nitrogen atom.

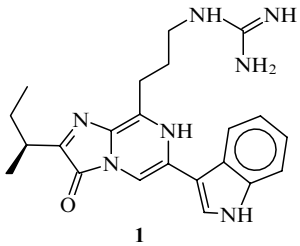


Although these compounds are seemingly simple, they have not been known until recently. The first representative of this class was described only in 1957.[1] However, during the next four decades, the chemistry of imidazopyrazines developed very intensely. Certainly, the attention of researchers was mainly focused on the elaboration of convenient methods for the synthesis of imidazopyrazines and on investigation of their chemical properties, physical properties, comprehensive spectroscopic characteristics and practical applications. A tremendous role in the development of the chemistry of imidazopyrazines belongs to the discovery of several imidazopyrazine-type luciferins that are responsible for the bioluminescence of various sea organisms. This discovery was followed by studies dealing with the elcudation of the structure of these luciferins and of the mechanisms of their bio- and chemiluminescence; these studies differed markedly from those described in traditional publications in the chemistry of imidazopyrazines. Synthesis of the so-called 'azacyclols' (products of cyclisation of activated esters of tripeptides) and other imidazopyrazines containing amino-acid residues as structural fragments was also significant. These studies can be regarded as an important link between the chemistry of imidazopyrazines, cyclic peptides and lysergine alkaloids.

The three general lines of research listed above have developed quite independently. If we formally judge the integrity of a field of investigation by the existence of scientific reviews, we find that the published reviews cover mostly the chemistry and the luminescence properties of imidazopyrazine-type luciferins (see, for example, Refs 2 – 4). To the best of our knowledge, the topic under consideration has been surveyed more broadly only in one review,[5] which was published in 1979. The above facts stimulated the author to compose a review devoted to the chemistry of imidazo[1,2-*a*]pyrazines. Related fused heterocyclic systems, for example, imidazo[1,2-*a*]quinoxalines,[6] are not analysed in this rewiew, due to their specific properties and special approaches required for their synthesis. The main purpose of this review was to discuss the methods for synthesis and reactions of imidazopyrazines (*i.e.* purely chemical aspects), whereas in considering their physicochemical features (spectra, structure, reaction kinetics, *etc.*) and practical applications, the author intended to provide readers with only a grasp of the data available from the literature.

II. Natural occurrence

As early as 1917, a bioluminescence reaction was discovered that involved luciferase and a luciferin with an unknown structure, which was isolated from sea crustacean of the genus *Cypridina*.[7] The structure of luciferin **1** was determined in the middle 60s by high-resolution field desorption mass spectrometry (MS), NMR and amino-acid analysis and was confirmed by its total chemical synthesis.[8 – 13]

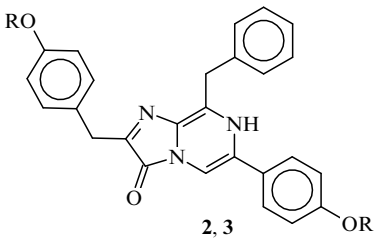


1

The molecule of coelenterazine **2** also incorporates the imidazopyrazine fragment.[14 – 16]

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Received 13 September 1996
Uspekhi Khimii **66** (3) 207 – 224 (1997); translated by Z P Bobkova



2, **3**

R = H (**2**), SO_3H (**3**).

Coelenterazine, in turn, is a prosthetic group of the luminescent protein aequorin,[16,17] which was first isolated from *Aequorea* medusas.[18] Coelenterazine is usually called '*Oplophorus* luciferin', because it can be isolated fairly conveniently from the shrimps *Oplophorus spinosus*. In general, this compound proved to be fairly abundant in the sea fauna. So far, coelenterazine has been found in the tissues of phosphorescent sea organisms, which belong to at least six different classes and range from the relatively primitive radiolaria to fishes.[19–30]

The third known luciferin, which accounts for the bioluminescence of the cephalopoda mollusks *Watasenia scintillans*,[15,31,32] is coelenterazine disulfate **3**.

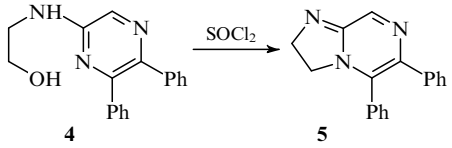
III. Synthesis

1. Construction of an imidazole ring based on pyrazine derivatives

The strategy involving synthesis of an imidazole ring, when a pyrazine ring is already present in the molecule, is most widely used for the synthesis of imidazopyrazines. This approach proved to be especially useful for the preparation of luciferins.

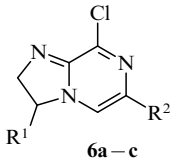
Depending on the nature of functional groups involved in cyclisation, several particular approaches can be distinguished.

The earliest approach to the synthesis of imidazopyrazines was based on cyclisation of *N*-(β-hydroxyethyl)aminopyrazine **4** under the action of thionyl chloride[1] to give 5,6-diphenyl-2,3-dihydroimidazo[1,2-*a*]pyrazine **5**.



4 **5**

Chlorodihydroimidazopyrazines **6a** – **c** were prepared in a similar way.[33,34]



6a – **c**

6	R^1	R^2	Yield (%)	Ref.
a	H	Cl	46	33
b	H	H	89	34
c	Me	H	45	34

Cyclisation of oxo-derivatives, obtained by oxidation of hydroxy-derivatives, in the presence of trifluoroacetic anhydride can be regarded as a modification of this method. 2,3-Dehydro-derivatives of compounds **6** were prepared in this way.[33,34] The scheme for the synthesis of imidazopyrazine analogues of nucleosides, for example, compound **7**,[35–37] also includes a stage of cyclisation of β-oxoalkylamines involving the N(1) atom of the pyrazine ring (Scheme 1).[37]

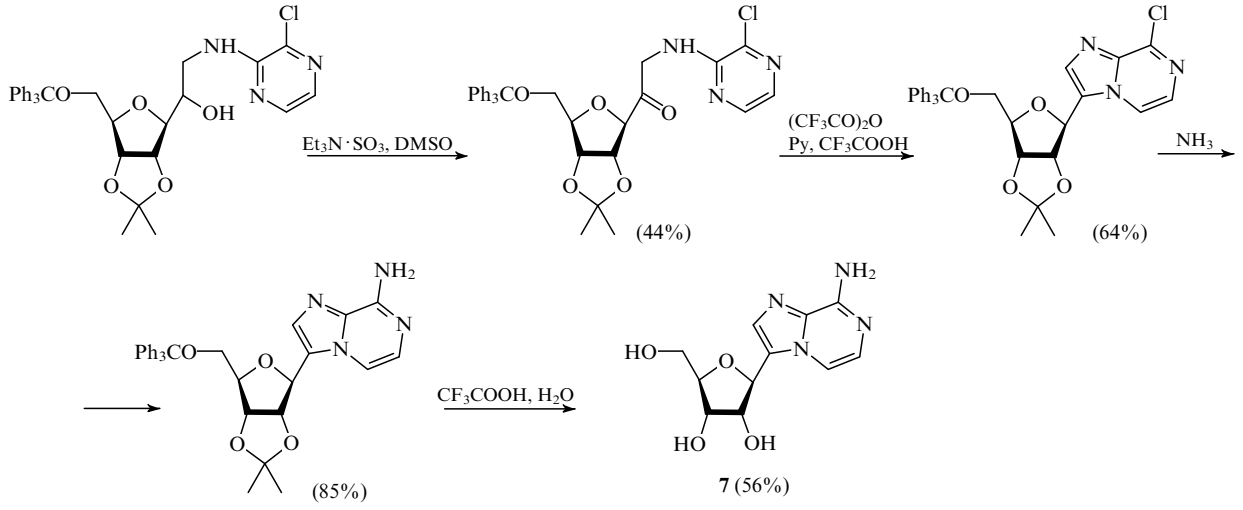
The use of *N*-(β-oxoethyl)aminopyrazine for the preparation of an analogue of 2,3-dihydroimidazopyrazine **5** devoid of phenyl substituents (yield 7%) has been reported.[38] The initial compound was introduced in the reaction as diethyl acetal, which was hydrolysed *in situ*.

Total synthesis of the luciferin **1** has been carried out according to Scheme 2.[10,39]

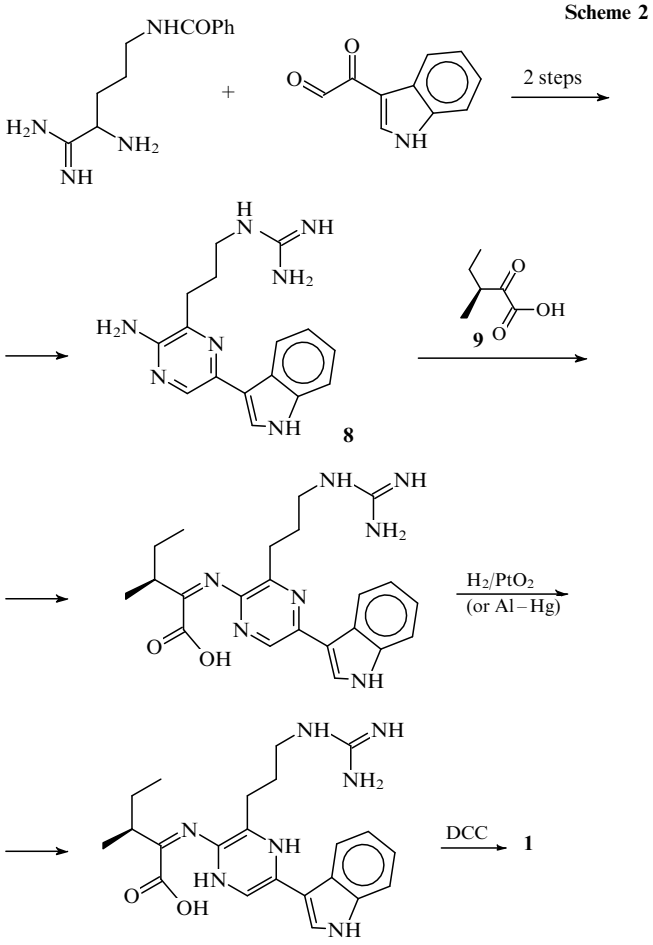
It is noteworthy that beginning from ethioluciferin **8**, the intermediates were not isolated and purified. The yield of the luciferin **1** obtained from ethioluciferin **8** was very low, < 1%.

Construction of an imidazole moiety based on α-oxoacids has also been used to prepare the natural coelenterazine (Scheme 3).[40] Two modifications of this method were described; according to procedure *A*, α-oxoacid **10** and aminopyrazine **11** were kept in a Bu^tOH – dioxane mixture at 140 °C for 25 min, which gave coelenterazine **2** (yield 49%) together with its dehydro-derivative **12** as a side product (yield 8.4%). According to procedure *B*, a mixture of the initial compounds **10** and **11** was kept in pyridine at 80 °C for 5 h, and this led to a pyrazinyl amino acid **13** in a yield of 49%. Treatment of the latter with a dehydrating agent (for example, Ac_2O) and then by $NaBH_4$ yielded the coelenterazine **2**.

Scheme 1

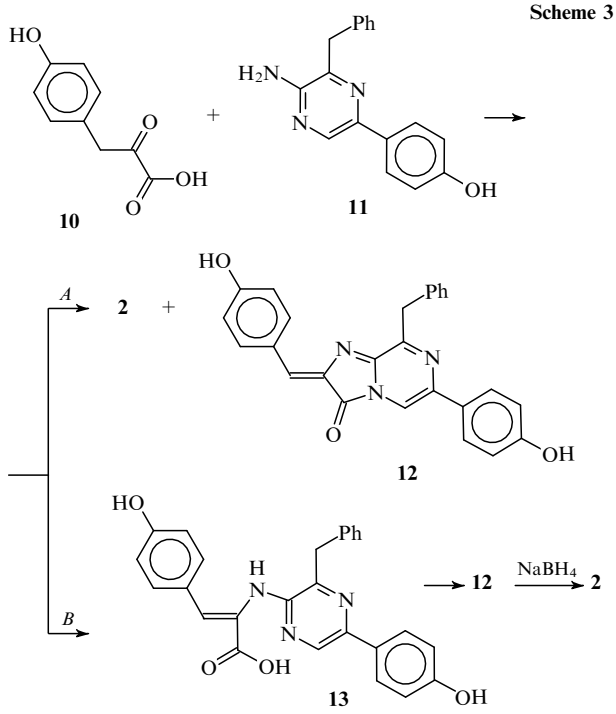


Scheme 2



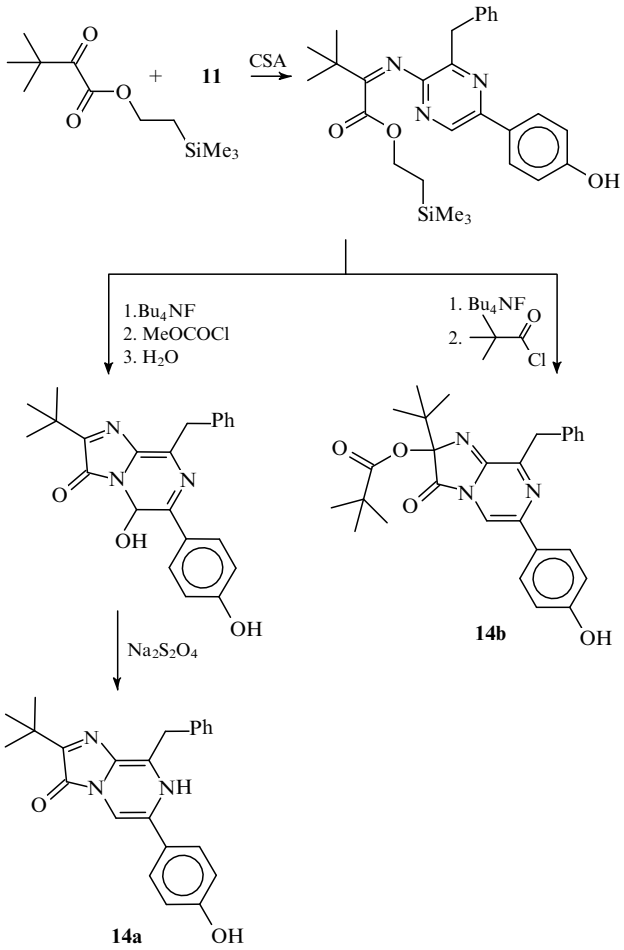
DCC is dicyclohexylcarbodiimide.

Scheme 3



The synthesis of compounds **14a** and **14b** (Scheme 4) in which an ester is used as the dicarbonyl component can be regarded as a specific case of the latter approach.[41]

Scheme 4

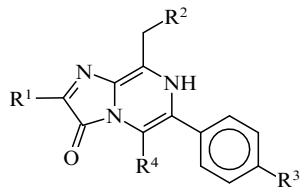


Where CSA is camphorsulfonic acid.

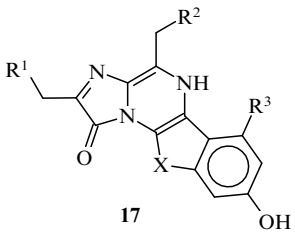
This approach has received no further development for the synthesis of luciferins or simpler imidazopyrazines.

The procedure for the synthesis of the luciferin **1** was markedly improved when a racemic α-oxoaldehyde, namely, 3-methyl-2-oxopentanal **15** was used in the reaction,[42,43] instead of the optically active α-oxoacid **9**. As a result, the yield of the luciferin increased to 30%. It is clear that the product obtained in this way exhibited no optical activity. Nevertheless, its bioluminescent activity proved to be nearly the same as that of the natural luciferin.

The same method based on condensation of aminopyrazines with glyoxals[42–45] made it possible to achieve impressing results in the synthesis of the coelenterazine **2** and its analogues.[15,41,46–53] The fruitfulness of this approach is clearly demonstrated by the diversity of compounds **16** and bridged analogues of coelenterazine **17** synthesised in this way. The structures of these products are presented in Tables 1 and 2. The bridged analogues **17** are formed in relatively low yields (normally ~10%), whereas the yields of compounds **16** reach 85%.



16



17

Table 1. Analogues of coelenterazine **16** obtained by cyclisation of aminopyrazines with glyoxals.

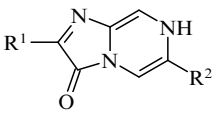
R^1	R^2	R^3	R^4	Ref.
Me	Ph	OH	H	52
Me	Ph	OMe	H	48
$PhCH_2$	Ph	OH	H	50
$PhCH_2$	Ph	OMe	H	47
p-$HOC_6H_4CH_2$	Ph	OH	H	15, 52
p-$HOC_6H_4CH_2$	Ph	NH_2	H	49
p-$FC_6H_4CH_2$	Ph	OH	H	51
m, *p*-$F_2C_6H_3CH_2$	Ph	OH	H	50
$C_6F_5CH_2$	Ph	OH	H	50
p-$ClC_6H_4CH_2$	Ph	OH	H	50
p-$BrC_6H_4CH_2$	Ph	OH	H	50
p-$IC_6H_4CH_2$	Ph	OH	H	50
β-$C_{10}H_6CH_2$	Ph	OH	H	50
p-$HOC_6H_4CH_2$	$Me(CH_2)_3$	OH	H	50
p-$HOC_6H_4CH_2$	Pr^i	OH	H	50
p-$HOC_6H_4CH_2$	cyclo-C_5H_9	OH	H	50
p-$HOC_6H_4CH_2$	cyclo-C_6H_{11}	OH	H	50
p-$HOC_6H_4CH_2$	cyclo-$C_6H_{11}CH_2$	OH	H	50
p-$HOC_6H_4CH_2$	*p*-FC_6H_4	OH	H	50
p-$FC_6H_4CH_2$	$Me(CH_2)_3$	OH	H	50
p-$FC_6H_4CH_2$	Pr^i	OH	H	50
$PhCH_2$	cyclo-C_5H_9	OH	H	50
p-$FC_6H_4CH_2$	cyclo-C_5H_9	OH	H	50
$PhCH_2$	cyclo-C_6H_{11}	OH	H	50
p-$FC_6H_4CH_2$	cyclo-C_6H_{11}	OH	H	50
p-$HOC_6H_4CH_2$	Ph	OH	Me	50, 51
p-$HOC_6H_4CH_2$	Ph	OH	$HO(CH_2)_2$	51
p-$HOC_6H_4CH_2$	Ph	OMe	H	51
p-$HOC_6H_4CH_2$	Ph	NMe_2	H	51
Ph	Ph	OH	H	52, 53
$Ph(CH_2)_2$	Ph	OH	H	52, 53
$Ph(CH_2)_3$	Ph	OH	H	52, 53
Bu^t	Ph	OH	H	41

Table 2. Bridged analogues of coelenterazine **17** obtained by cyclisation of aminopyrazines with glyoxals.

R^1	R^2	R^3	X	Ref.
p-HOC_6H_4	Ph	H	CH_2	49, 51
p-HOC_6H_4	Ph	H	CH=CH	49
p-HOC_6H_4	Ph	H	$(CH_2)_2$	49–51
Ph	Ph	H	$(CH_2)_2$	50
p-FC_6H_4	Ph	H	$(CH_2)_2$	50
p-HOC_6H_4	cyclo-C_6H_{11}	H	$(CH_2)_2$	50
Ph	cyclo-C_6H_{11}	H	$(CH_2)_2$	50
p-FC_6H_4	cyclo-C_6H_{11}	H	$(CH_2)_2$	50
p-HOC_6H_4	cyclo-C_5H_9	H	$(CH_2)_2$	50
Ph	cyclo-C_5H_9	H	$(CH_2)_2$	50
p-FC_6H_4	cyclo-C_5H_9	H	$(CH_2)_2$	50
p-HOC_6H_4	Ph	H	$(CH_2)_3$	51
p-HOC_6H_4	Ph	OH	$(CH_2)_2$	51

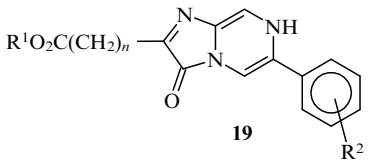
It can be seen from the above that considerable progress has been achieved in the chemical synthesis of coelenterazine, *Cypridina* luciferin and their analogues. Apparently, it should be expected that this line of research will be further developed. Nevertheless, another trend has appeared, and in the near future it may become a significant alternative to the chemical synthesis: recently, a synthesis of coelenterazine based on genetic engineering technique has been patented.[54]

The method based on the use of α-oxoaldehydes was found to be also convenient for the synthesis of simpler analogues of *Cypridina* luciferin, compounds **18**,[42–45] as well as of more complex derivatives **19**, which are used as probes for chemiluminescent immunoassay.[55]



18 (> 70%)

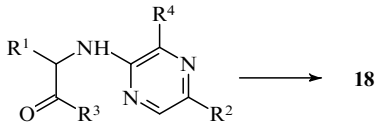
R^1 = Me, Ph;
R^2 = H, Me, Ph, *p*-$MeOC_6H_4$, 2-naphthyl, indol-3-yl



19

R^1 = H, Alk (C_{1-10}), succinimido;
R^2 = H, Alk (C_{1-4}), AlkO; n = 1–10

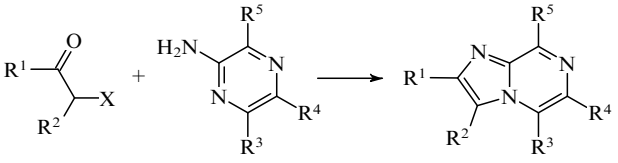
Another approach, which is based on cyclisation of pyrazinyl amino acids, their esters and amides and is similar to that shown in Scheme 1, also gives good results in the preparation of compounds **18**.[56–58]



R^1 = H, Me, Ph; R^2 = H, Ph;
R^3 = OH, NH_2, OMe, OEt; R^4 = H, Me.

The method in which aldehydes (as adducts with $NaHSO_3$) and KCN are used as building blocks for the imidazole fragment has found limited application. For example, it was used to prepare compound **18** (R^1 = R^2 = H); 3-aminoimidazo[1,2-*a*]pyrazine was formed as a side product.[59]

The method involving α-halocarbonyl intermediates (a special case of the Chichibabin reaction) has found the widest use in the synthesis of simple imidazopyrazines.[33, 34, 37, 60–87] Generally, this process can be represented by the following scheme:



20 **21**

If the α-halocarbonyl compounds are unstable (in particular, during storage), they can be introduced in the reaction mixture as the corresponding acetals and hydrolysed directly prior to the addition of 2-aminopyrazine **20** (see, for example, Refs 86 and 87). This synthesis is carried out in polar solvents (lower aliphatic alcohols or DMF) and usually with heating, but sometimes at room temperature. To bind the hydrogen halide liberated in the process, Na_2CO_3 or $NaHCO_3$ is added to the reaction mixture (before mixing of reactants or after completion of the reaction). A large number of imidazopyrazines **21** have been synthesised in this way; some examples are listed in Table 3.

In contrast to the approach described above, the method involving glyoxals, which was used advantageously for preparing luciferins and their analogues, does not enjoy wide popularity, for unknown reasons, in the synthesis of simpler imidazopyrazines. Only few examples describing the use of this method are documented. For example, synthesis of compounds of the type **18** with

Table 3. Imidazopyrazines **21 a – v** obtained by condensation of α-halocarbonyl compounds with 2-aminopyrazines **20**.

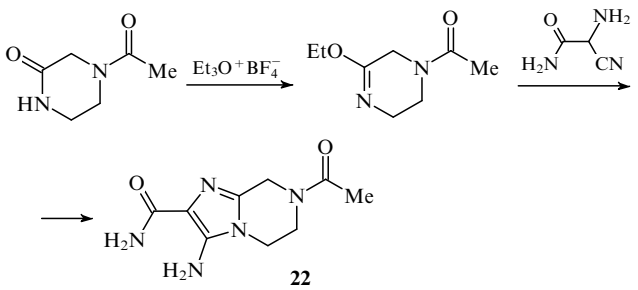
21 (see [a])	R^1	R^2 (see [b])	R^3 (see [b])	R^4	R^5 (see [b])	X	Yield (%)	Ref.
a	H	H	H	H	H	Br	41	63
						Cl	39	86
b	H	H	H	Cl	H	Br	68	33
c	H	Me	H	Cl	Br	Br	37	33
d	H	H	H	Ph	Br	Br	73	33
	H	Et	H	H	Cl	Br	59	34
	H	Et	Me	H	Cl	Br	59	34
	Ph	H	H	H	Me	Br	17	34
e	Me	H	H	H	H	Cl	15	61
						Br	20	71
f	H	Me	H	H	H	Br	25	71
						Cl	50	61
	H	H	OH(Cl)	Cl	NO_2	Br	66	66
	Ph	NO (NOH)	H Cl	H	H	Cl	55	68
	p-$O_2NC_6H_4$	NO (NOH)	H	H	H	Cl	60	68
g	H	H	H	Br	Br	Cl	45	71
h	CH_2Cl	H	H	H	H	Cl	45	71
i	CO_2Et	H	H	H	H	Br	30	71
j	H	H	H	H	CO_2Et	Br	10	71
k	CO_2Et	H	H	Br	Br	Br	40	71
l	CO_2Me	H	H	H	H	Br	10	71
m	CH_2CO_2Et	H	H	Br	Br	Cl	42	71
n	Me	H	H	H	Cl	Cl	37	78
o	Me	H	H	H	$PhCH_2O$	Cl	43	78
p	2,4-$(MeO)_2C_6H_3$	H	H	H	H	Br	6	80
q	2-MeO-4-MeS-C_6H_3	H	H	H	H (CO_2Me)	Br	9	80
r	2-MeO-4-$MeSO_2$-C_6H_3	H	H	H	Cl	Br	30	80
s	Me	Me	H	H	Cl	Br	4	82
t	*p*-MeC_6H_4	H	H	Cl	H	Br	3	83
u	H	$MeOCH_2$	H	Br	MeNH	Br	not given	87
v	H	$EtOCH_2$	H	Br	MeNH	Br	18	87

[a] Only those compounds which are considered below have been denoted by letters. [b] The substituent in the initial compound **20** is given in parentheses.

R^1 = Ph, *p*-$MeOC_6H_4$ and *p*-ClC_6H_4 and R^2 = H have been reported.[88,89] Compounds **21** with R^1 = *p*-$MeOC_6H_4$, R^2 = MeO, R^3 = R^5 = H, R^4 = Cl (**21w**); R^1 = Me, R^2 = OH, R^3 = R^4 = H, R^5 = OH (**21x**) have also been prepared in this way.[83,90]

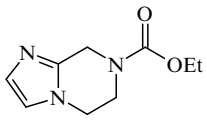
Other methods, in which the imidazole moiety is designed based on a six-membered ring present in the molecule, have been used only in a few studies. For example, treatment of 4-acetylpiperazin-2-one with triethyloxonium tetrafluoroborate followed by refluxing with α-amino-α-cyanoacetamide gave tetrahydroimidazopyrazine **22** (Scheme 5).[91,92]

Scheme 5

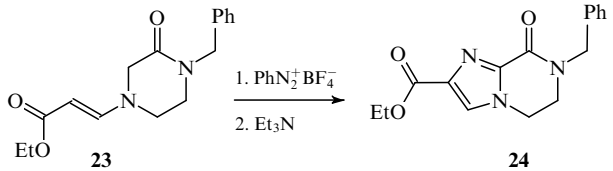


22

Another representative of the polyhydroimidazopyrazine series has been prepared in a similar way:[93]



Successive treatment of β-enaminoacrylate **23** with phenyldiazonium tetrafluoroborate and triethylamine yields tetrahydroimidazopyrazine **24**.[94]



23 **24**

Imidazopyrazine **21y** (R^1 = Me, R^2 = NH_2, R^3 = R^4 = H, R^5 = $PhCH_2O$) has been prepared by the reaction of 2-amino-3-(benzyloxy)pyrazine with acetaldehyde and sodium cyanide.[78]

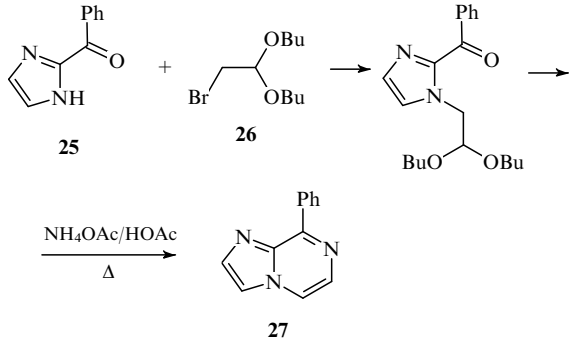
Condensation of 2,3-epoxybutanal with 2-aminopyrazine in the presence of alumina gives rise to 3-(1-hydroxyethyl)imidazo[1,2-*a*]pyrazine **21z** [R^1 = R^3 = R^4 = R^5 = H, R^2 = CH(OH)Me] in 26% yield.[95]

2. Construction of a pyrazine ring based on imidazole derivatives

Condensation of substituted imidazoles is used in the synthesis of imidazopyrazines much more rarely than the strategy considered in the previous Section.[96–104]

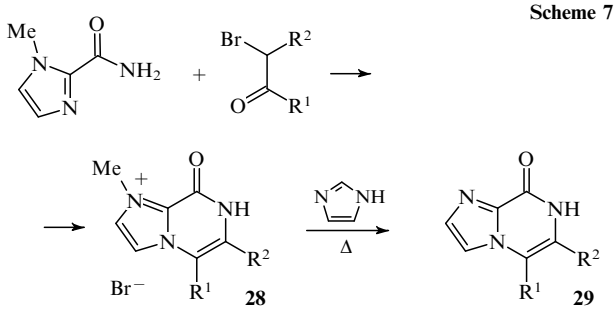
This approach was used for the first time by Russian researchers,[96] who synthesised 8-phenylimidazo[1,2-*a*]pyrazine **27** in 83% yield by the reaction of 2-benzoylimidazole **25**, which was used as the sodium salt, with bromoacetal **26** with subsequent refluxing of the product with ammonium acetate in acetic acid (Scheme 6).

Scheme 6



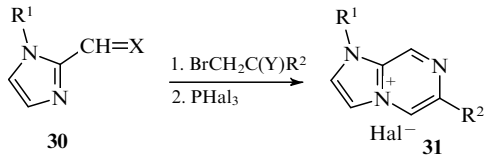
α-Halocarbonyl compounds enter into condensation with 1-alkylimidazole-2-carboxamides[97,99] to give intermediate imidazopyrazinium salts **28**; the latter can be converted into imidazopyrazin-8-ones **29** by refluxing in imidazole (Scheme 7):

Scheme 7



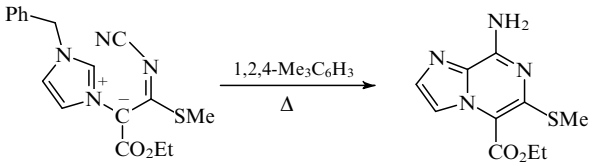
R^1 = H, Alk, Ph; R^2 = Ph, naphthyl, pyridyl, furyl.

Quaternisation of imidazole-2-carboxaldehyde ethylene acetals and oximes **30** upon treatment with α-halocarbonyl compounds and their oximes followed by deoxygenation of the intermediates thus formed with phosphorus trihalides has resulted in the formation of imidazopyrazinium salts **31**.[100]

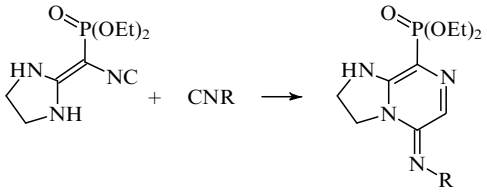


R^1 = Me, $PhCH_2$; R^2 = H, Me, Ph; X = NOH, $-O(CH_2)_2O-$; Y = O, NOH; Hal = Cl, Br.

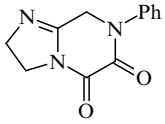
On refluxing in 1,2,4-trimethylbenzene, ylide **32** undergoes 1,6-cyclisation and simultaneous debenzylation and is thus converted into imidazopyrazine **33**.[102]



An interesting reaction of ketene *N*,*N*-acetals in which two isocyanide groups participate in the formation of a pyrazine ring has been reported.[103]



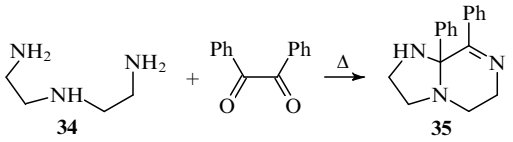
Finally, a 5,6-dioxoimidazopyrazine derivative has been synthesised by interaction of binucleophilic 2-(arylaminomethyl)imidazolines with oxalyl chloride.[104]



3. Simultaneous formation of imidazole and pyrazine rings from acyclic precursors

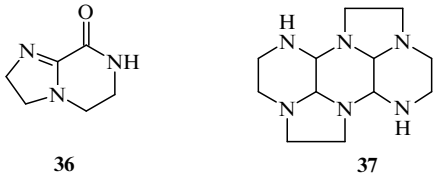
Methods for the synthesis of imidazopyrazines from acyclic precursors are used rather as rarely as those described in Section 2.

Recently, the reaction of diethylenetriamine **34** with dibenzoyl to give 1,2,3,5,6,8*a*-hexahydro-8,8*a*-diphenylimidazo[1,2-*a*]pyrazine **35** has been discovered.[105,107]

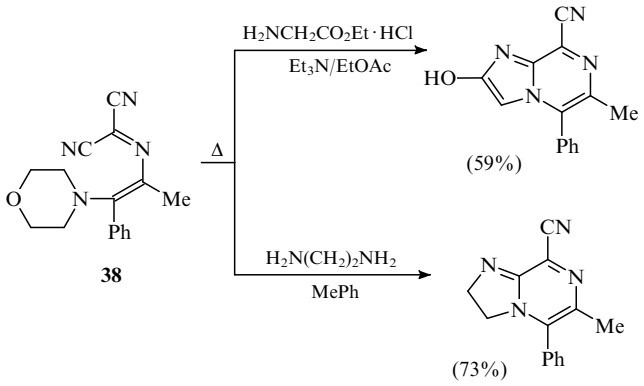


This reaction is carried out by refluxing the reactants in methanol in the presence of mercury(II) chloride (yield 60%).[107]

The same amine **34** condenses with diethyl oxalate to give imidazopyrazine **36**,[108] while its condensation with glyoxal or *N*,*N*′-dicyclohexylethylenediimine affords polycyclic polyamine **37** incorporating two imidazopyrazine structural fragments.[109]



Treatment of ethyleneimine **38** with the ethyl ether of glycine or ethylenediamine gives rise to substituted imidazopyrazines.[110,111]

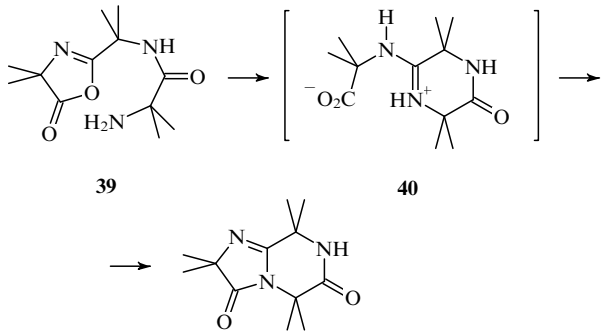


38

A special position in this group of methods belongs to the preparation of imidazopyrazines from tripeptide (usually linear) derivatives. This approach has been developed within the chemistry of amino acids and peptides, which stands apart from the chemistry of heterocyclic compounds; therefore, terminology peculiar to peptide chemistry has taken root in this line of research.

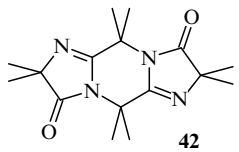
The formation of imidazopyrazines from derivatives of linear peptides was first described by Jones *et al.*[112, 113] It was found that the oxazolone derivative **39** of the tripeptide AIB–AIB–AIB (AIB is α-aminoisobutyric acid or α-methylalanine) readily isomersises (in ethyl acetate at room temperature) to give imidazopyrazine **41** in a high yield (95%). This reaction occurs presumably *via* the formation of monocyclic amidine **40** (Scheme 8).

Scheme 8



39 **40** **41**

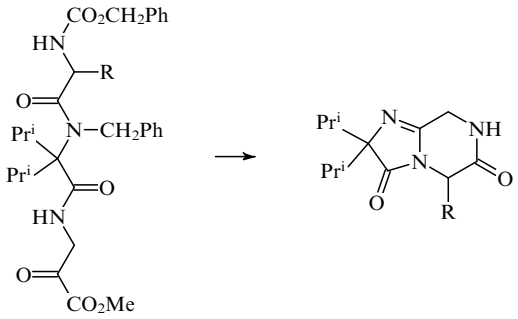
A conceptually similar method for the synthesis of the imidazopyrazine **41** involves treatment of AIB tri-, tetra- and penta-peptides with phosphorus pentachloride or thionyl chloride in acetyl chloride and subsequent cyclisation of the intermediate acid chlorides in pyridine.[114–117] The yields of the compound **41** obtained in this way are much lower (11%–26%). It is of interest that when tetra- and penta-peptides are used in this reaction, bis-imidazopyrazine **42** is formed simultaneously in a yield of 4%–10%.



42

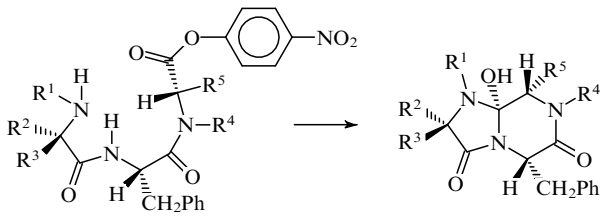
This method has also been used to prepare polydeuterated analogues of **41** and **42**.[115, 116]

The reactions described above reflect the specific stereochemistry of derivatives of α,α-dialkylamino acids (in particular, AIB), namely, a certain conformational rigidity of their carbon skeleton, and are not characteristic of ordinary natural amino acids. Nevertheless, methods for the preparation of the imidazopyrazines **41** containing Gly, Ala, Val, *etc.* as structural fragments have been developed. For example, catalytic hydrogenolysis of carbobenzoxy-derivatives of methyl esters of tripeptides[118] makes it possible to synthesise the imidazopyrazines of the type **41** incorporating Gly, Ala, Val, Leu and Phe residues.



R = H, Me, Pr^i, Bu^i, CH_2Ph.

Cyclisation of activated esters of tripeptides has been studied in detail by Italian researchers.[119–128] However, although the compounds obtained in these studies belong to the same class of imidazo[1,2-*a*]pyrazines, they possess an important feature distinguishing them from the amidines **41**: their molecules incorporate a C(8*a*)OH–N(1)R^1 fragment instead of the C(8*a*)=N(1) fragment. Therefore, these compounds were called 'azacyclols'. As a rule, they are synthesised starting from 4-nitrophenyl esters of tripeptides **43**. According to a typical procedure, tripeptide **43** is kept in a 1 : 1 mixture of dioxane and an aqueous carbonate buffer solution (0.1 M $NaHCO_3$ + 0.1 M Na_2CO_3, 1 : 1) for 1–2 h at room temperature. Characteristics for a number of imidazopyrazines **44** obtained in this way are listed in Table 4.



43 **44**

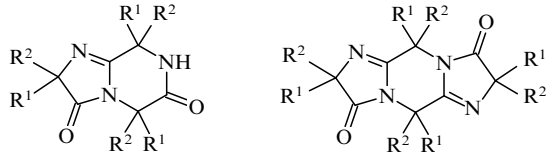
Undoubtedly, it is the mild conditions used in this reaction that account for the preservation of the C(8*a*)OH group in the molecule; otherwise (at elevated temperatures) one should expect that elimination of a water molecule would occur to give the amidine analogues of **41**.

Table 4. Azacyclols **44** obtained by cyclisation of *p*-nitrophenyl esters of the tripeptides **43**.

R^1	R^2	R^3	R^4	R^5	Yield (%)	Ref.
$PhCH_2OCO$	Me	H	$-(CH_2)_3-$		70	119
p-$BrC_6H_4CH_2OCO$	Me	H	$-(CH_2)_3-$		50	119
$PhCH_2OCO$	$=CH_2$		$-(CH_2)_3-$		80	120
$CH_2=CHCH_2OCO$	Me	H	$-(CH_2)_3-$		45	121
$PhCH_2OCO$	Me	H	$-(CH_2)_2-$		not given	122
$PhCH_2OCO$	Me	H	Me	H	—	122
$-(CH_2)_3-$ [a]		H	$-(CH_2)_3-$		8.5	123
H [a]	Me	H	$-(CH_2)_3-$		—	124
$-COCH_2SCH_2-$ [b]		H	$-(CH_2)_3-$		50	125, 126

[a] As a salt with CF_3COOH. [b] In the initial tripeptide, R^1 = $ClCH_2CO$, R^3 = CH_2SSBu^t; the protection was removed *in situ* during the cyclisation (Bu_3P and $NaHCO_3$ in aqueous propanol).

Taking into account the fact that amino-acid residues are the main structural units of the molecules **41** and **44**, it would be reasonable to suggest that these imidazopyrazines could, in principle, also be obtained by intermolecular cyclisation of amino acids or their activated derivatives. However, syntheses of the imidazopyrazines **41** and **44** based on this strategy have not yet been developed. Nevertheless, in a study of the products of high-temperature (200–250 °C) condensation of vaporised amino acids (Ala, Val, Nva, and Leu) catalysed by silica gel,[129–131] some compounds, dehydrated to a greater extent than cyclic dipeptides (piperazine-2,5-diones), have been detected. The latter are often called 'amino acid anhydrides', because they can be obtained directly from amino acids (although this is seldom used for practical purposes). Hydrolysis of these compounds leads to the recovery of the amino acids. Whereas the formation of piperazine-2,5-diones is accompanied by elimination of one water molecule per amino acid molecule (the same 1 : 1 ratio is retained in the case of other cyclic peptides), the products under consideration[129–131] were found to be dehydrated to a greater extent than the corresponding piperazine-2,5-diones. The ratio of the number of amino-acid residues constituting these molecules to the number of water molecules eliminated upon dehydration is 3 : 4 and 4 : 6. Studies carried out by fast atom bombardment mass spectrometry,[129] HPLC/MS and GLC/IR/MS with computer simulation of the IR spectra[130, 131] have permitted these compounds to be identified as imidazopyrazines and bis-imidazopyrazines.

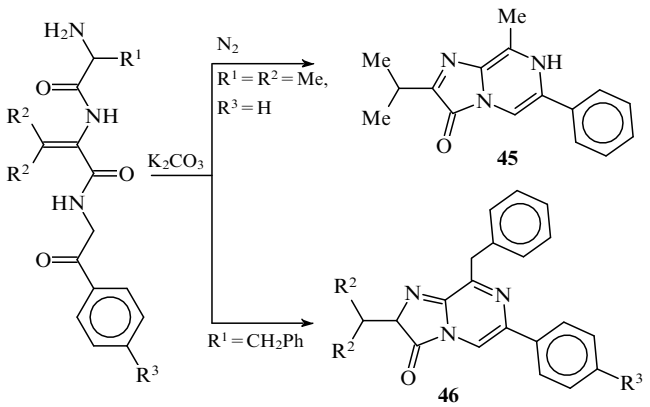


R^1 = H, R^2 = Me(Ala), Pr^i(Val), Pr^n(Nva), Bu^i(Leu).

The AIB derivatives **41** and **42** ($R^1 = R^2$ = Me) mentioned above also belong to this class of compound. According to tentative estimates, the yield of imidazopyrazines can reach 20%; however, they are strongly contaminated by products of thermal destruction that occurs immediately after their formation. Thus, the reactions in question can hardly be of any synthetic value.

Some studies, mostly directed at the modelling of the biosynthesis of the imidazopyrazine-type luciferins, have been reported.[132, 133] The researchers suggested that modified tripeptides are biosynthetic precursors of all luminescent systems (coelenterata, crustacean, *etc.*). This suggestion was supported by the successful synthesis of compounds **45**[132] and **46**[133] — analogues of the *Cypridina* luciferin and of coelenterazine — carried out according to Scheme 9.

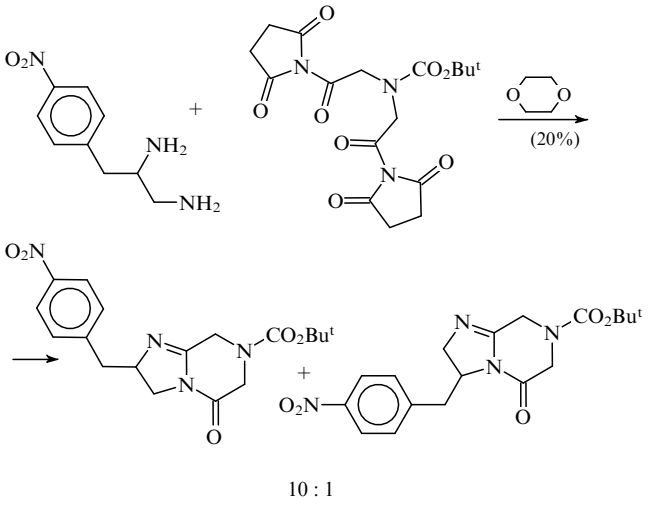
Scheme 9



R^2 = Me: R^3 = OCH_2Ph, OH, H;
R^2 = H; R^3 = OH, H.

A typical procedure consists in heating of tripeptide-like compounds in DMF in the presence of K_2CO_3. In the case of the compound **45**, cyclisation was carried out under an inert atmosphere (N_2; yield 58%).

The last case the author is aware of, where the imidazole and pyrazine rings are formed simultaneously from acyclic precursors is rather an occasional observation in the field of synthesis of polyaza-containing macrocyclic ligands. Condensation of (4-nitrobenzyl)ethylenediamine with *N*,*N*′-[*N*-(*tert*-butoxycarbonyl)iminodiacetyl]disuccinimide afforded a mixture of two isomeric imidazopyrazines instead of the expected 9-membered macrocyclic diamide.[134]



10 : 1

4. Introduction and modification of substituents in the imidazopyrazine nucleus

Halogenation[33, 34, 71, 86, 135, 136] of the imidazopyrazine nucleus is the most important reaction among those involving the imidazopyrazine system, since it permits not only introduction of halogen atoms into this nucleus but also their subsequent replacement by other substituents.

Treatment of unsubstituted imidazo[1,2-*a*]pyrazine (**21a**; Table 3) with bromine in glacial acetic acid results in its bromination in the 3- and 5-positions.[71, 135, 136] The yields of 3-bromo-, 5-bromo- and 3,5-dibromo-derivatives are 5%, 81% and 5%, respectively.[71]

Better selectivity is achieved with *N*-bromosuccinimide. Using the imidazopyrazines **21a** and **21g** as examples, it has been shown that bromination involves the 3-position, the corresponding products being formed in 44–72% yields.[86, 136] However, when *N*-bromosuccinimide is made to react with 8-(4-*tert*-butoxycarbonylpiperazino)imidazo[1,2-*a*]pyrazine,[34] substitution at C(5) predominates (the yield of the 5-bromo-derivative is 55%), and only with excess *N*-bromosuccinimide is the 3,5-disubstituted product formed (yield 59%).

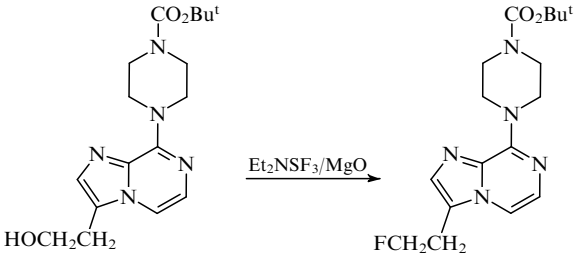
Conversely, reactions of the imidazopyrazine **21b** and 8-bromo-6-chloroimidazo[1,2-*a*]pyrazine with *N*-chlorosuccinimide lead to 3-chloro-derivatives in 72% and 90% yields, respectively.[33]

Exhaustive chlorination can be achieved by using phosphorus pentachloride. For example, the imidazopyrazine **21a** is converted into 2,3,5,6,8-pentachloroimidazo[1,2-*a*]pyrazine (55%),[86] and **21i** gives 3,5,6,8-tetrachloro-derivative (10%).[71]

When 6,8-dichloro-3-methylimidazo[1,2-*a*]pyrazine was refluxed with NaBr/HBr in butanone,[33] selective substitution of the chlorine atom at the 8-position by a bromine atom occurs (the 6-chlorine atom being retained). The yield of 8-bromo-derivative was 67%.

Finally, when 3-(2-hydroxyethyl)-8-(4-*tert*-butoxycarbonylpiperazino)imidazo[1,2-*a*]pyrazine **47** was treated with diethylaminosulfur trifluoride in the presence of magnesium oxide as a

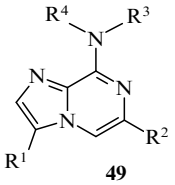
catalyst, the hydroxy-group was replaced by a fluorine atom,[34] which resulted in the synthesis of fluoro-derivative **48**.



47 **48** (41%)

As noted above, substitution of halogen atoms is a convenient method for introducing other substituents into the imidazopyrazine nucleus. This substitution is used most frequently to introduce amino-groups.

This reaction is fairly selective; when the nucleus contains halogen atoms at the 3- and 8-positions or the 6- and 8-positions, substitution involves only the 8-halogen atom to give compounds **49a**–**i** (Table 5).[33, 34, 65, 87, 135, 137]



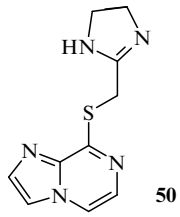
49

The NH group in the piperazine ring is protected by introducing a *tert*-butoxycarbonyl group (compounds **47**, **48** and **49 l**, **m**).[34]

Table 5. Imidazopyrazines **49a – m** obtained by substitution of amino-groups for the bromine atom at the 8-position.

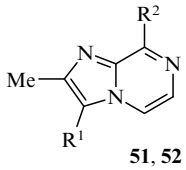
49	R^1	R^2	R^3	R^4	Ref.
a	Br	H	H	H	87
b	Br	H	H	Me	87
c	Br	H	H	Et	87
d	H	Br	H	H	87
e	H	Br	H	Me	87
f	H	Br	H	Et	87
g	H	Br	$-(CH_2)_2O(CH_2)_2-$		87
h	H	Cl	$-(CH_2)_2NH(CH_2)_2-$		65
i	Me	Cl	$-(CH_2)_2NH(CH_2)_2-$		33
j	H	Ph	$-(CH_2)_2NH(CH_2)_2-$		33
k	H	H	$-(CH_2)_2NMe(CH_2)_2-$		34
l	H	Me	$-(CH_2)_2N(CO_2Bu^t)(CH_2)_2-$		34
m	Me	Me	$-(CH_2)_2N(CO_2Bu^t)(CH_2)_2-$		34

Substitution of the halogen atoms has also been used in the synthesis of a series of 8-(2-imidazolylmethoxy)-, 8-(2-imidazolylmethylthio)- and 8-(2-imidazolylmethylamino)imidazo[1,2-*a*]pyrazines.[138] For example, treatment of 8-chloroimidazo[1,2-*a*]pyrazine with thiourea followed by hydrolysis of the product with potassium carbonate has given a 8-sulfanyl-derivative, which has been converted into imidazopyrazine **50** by the reaction with sodium methoxide and 2-chloromethyl-2-imidazoline.



50

Treatment of the 8-chloroimidazopyrazines **21e** and **21s** with Grignard reagent (phenethylmagnesium bromide) and copper(I) phenylacetylenide has given the corresponding substituted imidazopyrazines **51** and **52**.[78, 82]



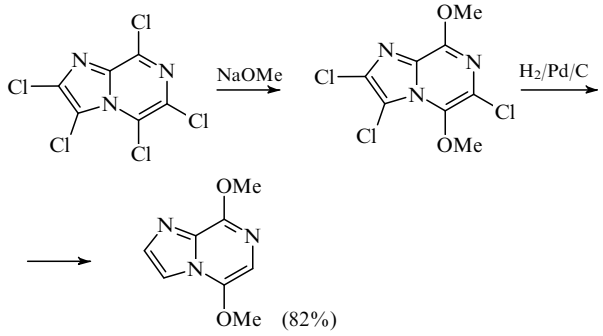
51, **52**

51: R^1 = H; R^2 = CH_2CH_2Ph (62%);
52: R^1 = Me; R^2 = C≡CPh (68%).

The ethynyl group in the compound **52** can be reduced to the vinyl group (yield 41%) by hydrogenation in the presence of the Lindlar catalyst (lead-poisoned 5% $Pd/CaCO_3$).[82]

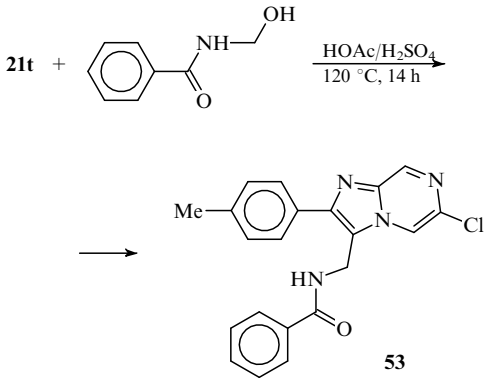
Substitution of the chlorine and bromine atoms by methoxy-groups can be accomplished by treatment with sodium methoxide.[86, 136] In the case of polyhaloimidazopyrazines, the halogen atoms at the 5- and 8-positions are replaced predominantly. It was not specified in this study, which of these two positions is preferentially attacked. The remaining halogen atoms can be removed by hydrogenation in the presence of Pd/C (Scheme 10).[86, 136]

Scheme 10



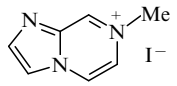
However, in the case of 6,8-dibromoimidazo[1,2-*a*]pyrazine, only the 8-bromine atom is substituted, whereas the 6-bromine atom remains unaffected, and the reaction yields 6-bromo-8-methoxyimidazo[1,2-*a*]pyrazine.[136]

Other substituents can also be introduced in the imidazopyrazine nucleus. For example, when unsubstituted imidazo[1,2-*a*]-pyrazine **21a**[139] and 6-bromo-8-methoxyimidazo[1,2-*a*]pyrazine[87] react with formaldehyde, regioselective hydroxymethylation in the 3-position occurs. Nitrosation of 8-(benzyloxy)-2-methylimidazo[1,2-*a*]pyrazine (**21o**) with sodium nitrite followed by reduction of the nitroso-derivative with metallic zinc resulted in the introduction of an amino-group in the 3-position of this compound.[78] Synthesis of 3-benzamidomethyl derivative **53** has been reported.[83]

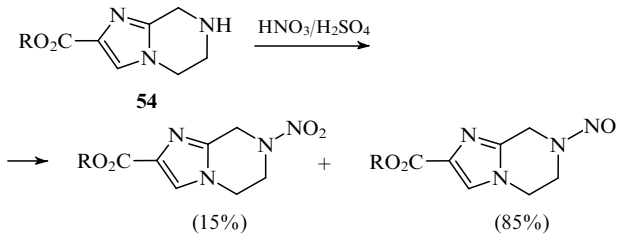


53

Alkylation of the pyrazine nitrogen atom has also been used for synthetic purposes. Thus treatment of the compound **21a** with MeI (methanol, 5 days, room temperature) affords imidazopyrazinium salt in 11% yield.[136]

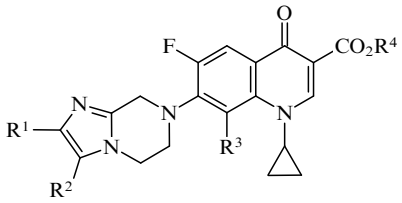


Nitrosation and nitration of tetrahydroimidazopyrazines **54** also involves the N(7) atom,[70] and treatment with HNO_3/H_2SO_4 leads to a mixture of 7-nitro- and 7-nitroso-derivatives.



R = Me, Et.

Similarly, a series of 7-substituted derivatives **55** have been obtained by arylation of tetrahydroimidazopyrazines **54**.[140–142]

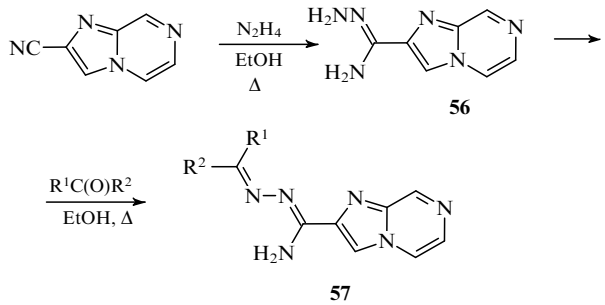


55

R^1, R^2 = H, Alk, Ph; R^3 = Hal; R^4 = H, Alk.

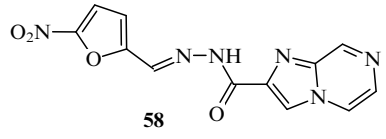
The esters **21i**,**k**,**l** can be hydrolysed to the corresponding carboxylic acids or converted into the corresponding amides by reaction with NH_4OH (or into hydrazides by reaction with N_2H_4) and then into nitriles by treatment with $POCl_3$.[71] The latter were successively converted into amidrazones **56** and **57** according to Scheme 11.[71,143]

Scheme 11



R^1 = H, Me; R^2 = Me, Ac, Ph, *p*-$O_2NC_6H_4$, anisyl, furyl;
R^1R^2 = $-(CH_2)_5-$.

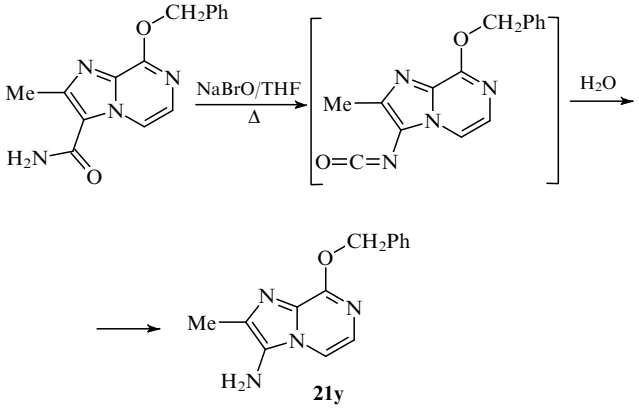
Further functionalisation of the hydrazide has resulted in the synthesis of nitrofuran derivative **58**.[144]



58

It is possible to convert amides into the corresponding amines as has been demonstrated by the synthesis of the imidazopyrazine **21y** (Scheme 12).[145]

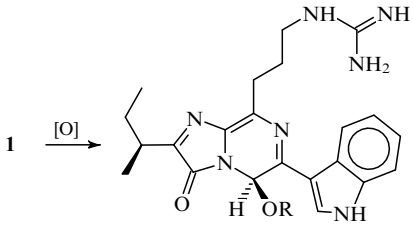
Scheme 12



21y

Substitution of the 2-chloromethyl groups in the imidazopyrazine nucleus by hydroxymethyl groups (refluxing in an aqueous solution of Na_2CO_3)[71] and substitution of 2-benzoyloxyethyl groups by hydroxyethyl groups (refluxing in a solution of $MeNH_2$ in aqueous methanol)[34] have been reported. 8-Methoxy groups are replaced by methylamino-groups on refluxing in an aqueous solution of $MeNH_2$.[87] Imidazopyrazine **21z** [R^1 = R^3 = R^4 = R^5 = H; R^2 = CH(OH)Me] is oxidised by manganese(IV) oxide to give the corresponding ketone.[95]

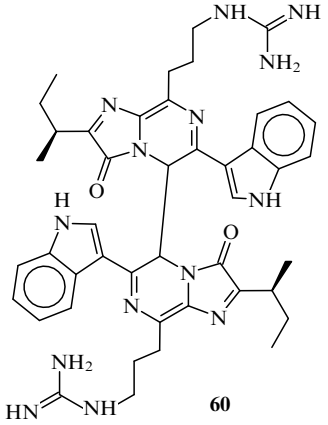
Among the reactions involving natural imidazopyrazine luciferins and their analogues, oxidation of the luciferin **1** to luciferyls **59** is noteworthy.[146]



59

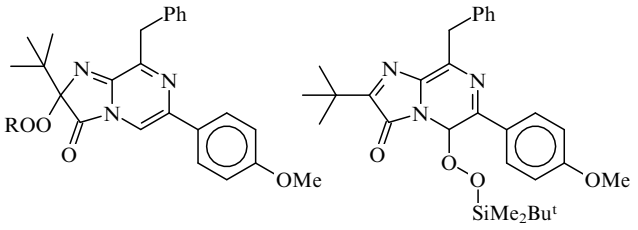
R = H, Me, Pr^i, Bu^n.

When alcohols are used as solvents and PbO_2 is used as the oxidising agent, the reaction yields luciferyl ethers **59** (R = Alk). The corresponding alcohol **59** (R = H) can be obtained by oxidation under milder conditions: with diphenylpicrylhydrazyl as the oxidizing agent and in aprotic media (for example, DMF). In the latter case, dimeric biluciferyl **60** is formed as an intermediate product. This compound can be isolated when the luciferin **1** is oxidised with $K_3[Fe(CN)_6]$.[147] Reduction of the compounds **59** (R = H) and **60** with $Na_2S_2O_4$ recovers the initial luciferin **1**.[146,147]



60

Introduction and/or modification of side substituents in the existing imidazopyrazine nucleus has been used in the synthesis of coelenterazine analogues. For example, radical oxidation of the *O*-methyl derivative of the compound **14a** involving the 2-position [148, 149] or the 5-position [150] gives rise to the following peroxide derivatives:



R = Me_3C, Me_3Si.

The 4′-methoxy-groups themselves in the *O*-methyl derivative of the compound **14a** and other compounds of this type often play only a protective role and can be subsequently removed by treatment with pyridine hydrochloride at 210 °C for 2 h under an argon atmosphere.[48] In addition, free phenolic groups can be protected by acetylation with acetic anhydride in the presence of catalytic amounts of H_2SO_4.[151] This approach has been used in the synthesis of the β-D-glucuronopyranoside of coelenterazine **61**,[23] which exhibits bioluminescent properties (Scheme 13).

Treatment of coelenterazine with acetic anhydride in the presence of catalytic amounts of concentrated sulfuric acid at room temperature has led to its tri-*O*-acetyl derivative (yield 86%).[60] The subsequent selective hydrolysis and treatment with the Py · SO_3 complex in pyridine at room temperature resulted in the substitution of the enol residue at the imidazole ring by a sulfate group. The two remaining acetate groups were selectively eliminated. These reactions resulted in the synthesis of coelenterazine enol monosulfate.[60]

IV. Reactions

The methods for the synthesis of imidazopyrazines involving introduction or modification of side groups, considered in the previous Section (III.4), give a good idea of the reactions known for imidazopyrazines, despite the fact that the studies considered have been devoted just to the development of synthetic procedures. The reactions that have received no practical use have not been studied systematically, except for the study of mechanisms of luminescence of luciferins (see below).

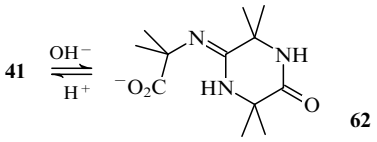
The reaction of the imidazopyrazine **21a** with hydrazine leads to a mixture of 2-methylimidazole and 1-ethyl-2-methylimidazole in a ratio of 5 : 4.[63] It was thus suggested that the reaction mechanism includes the attack by hydrazine either at the 5-position or at the 8-position of the imidazopyrazine molecule (Scheme 14).

Phenyllithium reacts with the compound **21a** yielding 8-phenyl-substituted derivative **27** and 5,6-dihydro-8-phenylimidazo[1,2-*a*]pyrazine in a ratio of 1 : 3.[152] Methyllithium reacts with the imidazopyrazine **21a** in a similar way.[153]

It has been found that, unlike imidazo[1,2-*a*]pyrimidine and imidazo[1,2-*c*]pyrimidine, 2- and 3-methylimidazo[1,2-*a*]pyrazines do not undergo the Dimroth rearrangement.[61, 154]

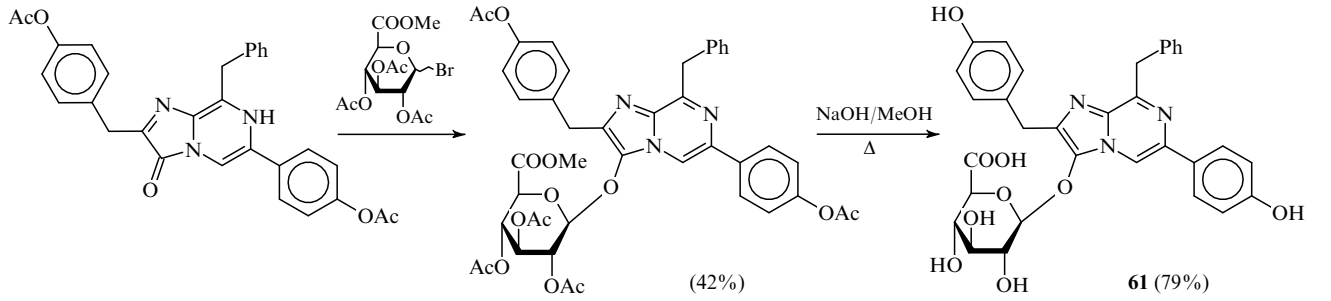
Catalytic hydrogenation of the bis-imidazopyrazine **37** leads to *N*-(2-aminoethyl)pyrazine.[109]

The behaviour of the imidazopyrazine **41** during hydrolysis has been studied.[115] Although the molecule of this compound incorporates amino-acid structural fragments and, hence, it resembles somewhat cyclic peptides, the compound **41** proved to be much more resistant to hydrolysis than peptides. For example, hydrolysis of **41** in alkaline aqueous methanol stops at the stage of formation of 'amidino-acid' salt **62**, which is readily converted into the initial compound **41** in acid or even in neutral solutions.

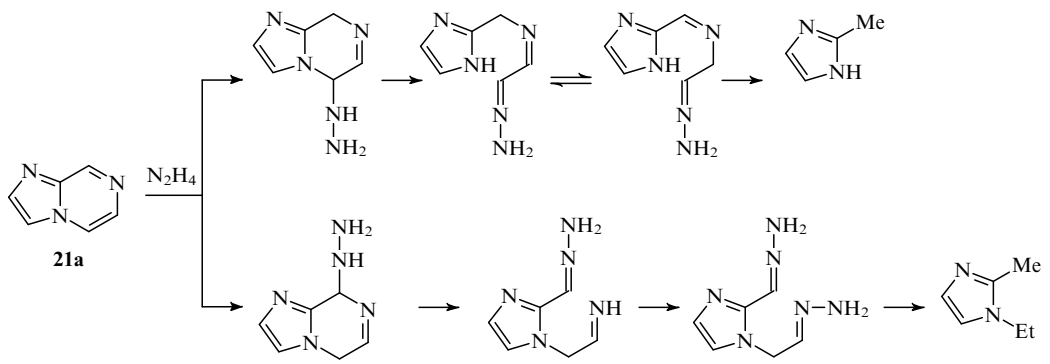


62

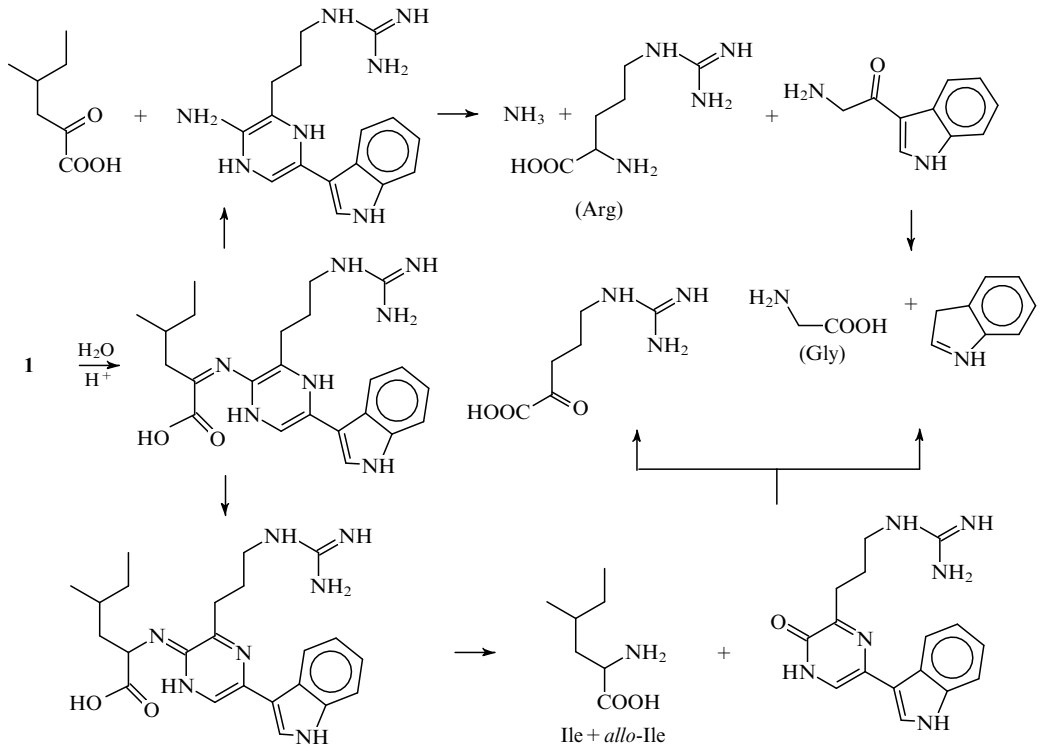
Scheme 13



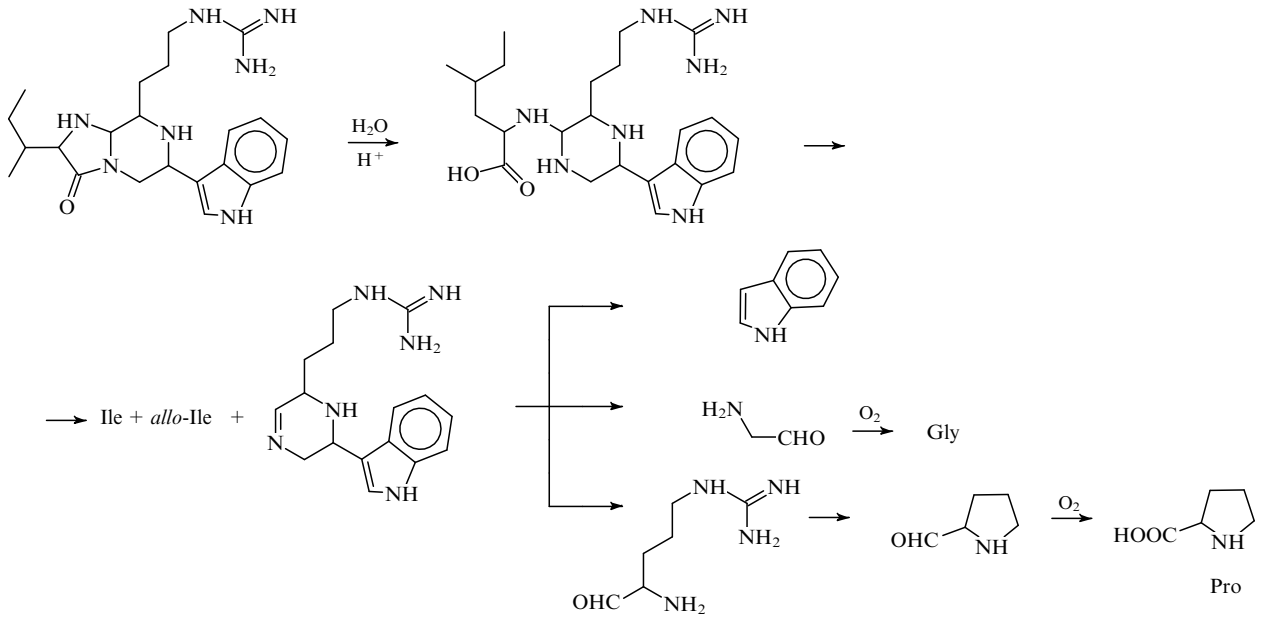
Scheme 14



Scheme 15



Scheme 16

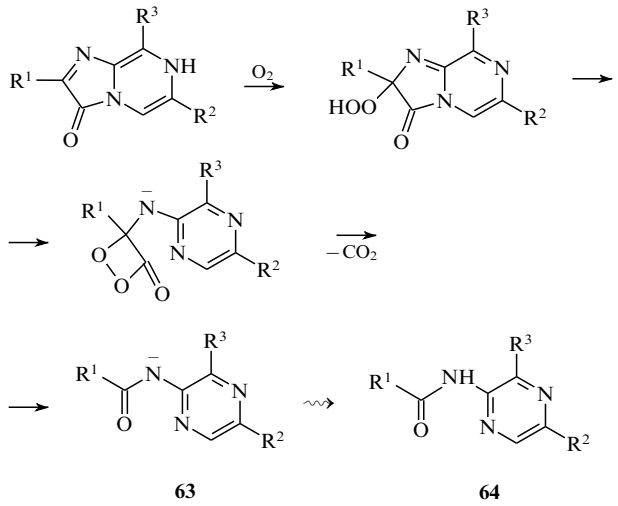


In order to determine the structure of the luciferin **1**, products of its hydrolysis as well as those of hydrolysis of its 1,2,5,6,7,8-hexahydro-analogue (6 M HCl at 100 °C) have been analysed.[8,9] The amino acids Gly, Arg, Ile and *allo*-Ile and γ-guanidino-α-oxobutanoic acid were detected in hydrolysates obtained from the luciferin **1**, while hydrolysates obtained from its hexahydro-analogue contained Gly, Pro, Ile and *allo*-Ile. Based on these results, the researchers proposed mechanisms for the hydrolysis of these compounds (Schemes 15 and 16).

The most complex problem in the investigation of reactions of imidazopyrazines was to elucidate the mechanism of luminescence (bio- and chemiluminescence in various molecular systems) of luciferins and their analogues. Studies along these lines were started more than 30 years ago. The results of these studies have been reported in a vast number of papers and reviews.[2–4, 16, 17, 45, 47–49, 51–53, 58, 59, 133, 148, 155–189] However, at present, specialists admit that the molecular mechanism is 'still unclear', and the problem is discussed within the framework of a 'working hypothesis' (see, for example, Ref. 148).

Nevertheless, based on the accumulated data, it was concluded that the chemiluminescence of the luciferin **1**, coelenterazine and their synthetic analogues containing a 3,7-dihydroimidazo[1,2-*a*]pyrazin-3-one structural fragment (the compounds **14**, **16**–**18**, **45** and **46**) obeys identical rules, and its simplified mechanism is presented below (Scheme 17):[47, 58 148, 158, 161, 167]

Scheme 17



63 **64**

Light is emitted by the excited anion **63** of oxyluciferin **64** (or of coelenteramide in the case of luminescence of coelenterazine), and the latter can be isolated in a pure state after the completion of the reaction. Chemiluminescence is observed in aprotic solvents (1,2-dimethoxyethane, acetonitrile, dichloromethane, DMSO, *etc.*) in the presence of bases. For bioluminescence of the luciferin **1** and its analogues, the presence of luciferase is needed. As has already been noted, coelenterazine is a prosthetic group of the calcium-binding protein aequorin, bioluminescence of which is induced by introduction of calcium ions.[16,17,49,148]

The efficiency of chemiluminescence has been investigated and rate constants for the reaction of analogues of the luciferin **1** with peroxide anion and singlet oxygen in various molecular systems have been determined in some other studies.[19–21,201]

V. Spectral and some other properties

Publications dealing with the synthesis and reactions of imidazopyrazines, like any traditional studies in the organic chemistry, include characterisation of compounds obtained by NMR, UV and IR spectroscopy, MS and X-ray diffraction. Therefore, the reader interested in this topic can find this information in the original publications.

However, some papers, especially devoted to spectra and structural studies of individual imidazopyrazines, have also been published. For example, among the studies dealing with the spectra (mostly luminescent) properties of luciferin considered in the previous Section, Refs 16 and 16 should be distinguished; in these studies, tautomerism of natural luciferin and their analogues was studied in detail by NMR and UV spectroscopy. Mass spectrometry played a significant role in elucidating the mechanism of luminescence of these compounds.[9,13,176]

Some physical methods of analysis (UV, IR and NMR spectroscopy and MS) have been invoked to confirm the unusual structure of the cazacyclol **44**.[11,91,128] In addition, papers especially devoted to X-ray diffraction studies of these compounds have been published.[202,203] The structure of 1,2,3,5,6, *a*-hexahydro-8, 8-diphenylimidazo[1,2 *a*]pyrazine **35** has also been characterised by X-ray diffraction data.[107]

The use of NMR (usually ^{1}H NMR) spectroscopy to investigate various aspects of the structure and reactivity of imidazopyrazines has been reported.[61,86,88,89,204–208] The structural conditions for the Dimroth rearrangement have been determined for a series of imidazopyrazines (including the compounds **21e,f** which do not enter into this rearrangement).[61] The sites of protonation and tautomeric equilibria for a number of compounds of the type **18** and **21** have been studied by ^{1}H NMR,[88,89] ^{13}C NMR,[205,206] and ^{15}N NMR[205] spectroscopy. A correlation between the position of the ring nitrogen atoms in various azoloazines (including the imidazopyrazine **21a**) and the corresponding chemical shifts has been established.[207] Yet another application of NMR spectroscopy (^{1}H and ^{15}N) has been the determination of the sites of nucleophilic substitution in the molecules of the imidazopyrazines **21**.[86,204,208]

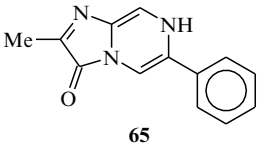
The sites of protonation of the molecule **21a** have been determined using magnetic circular dichroism[209] and UV spectroscopy.[38] The electronic structure of this compound (among other fused 5- and 6-membered aza-heterocycles has been discussed based on the data of UV spectroscopy.[210,211]

VI. Applications

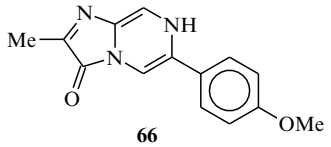
It is not exaggeration to say that luciferin, coelenterazine **2** and their synthetic analogues possess the most unusual properties among all known imidazo[1,2 *a*]pyrazines. Their ability to luminesce under the action of oxidants and the influence of various factors on this process permitted the development of a number of fairly specific analytical procedures.

In particular, luciferin and its synthetic analogues have been used for chemiluminescent determination of peroxides (including organic),[212–219] oxygen,[220] oxidase,[221] peroxidase,[222] glucose oxidase,[223] galactosidase[224] and ATP;[225] for investigations of the reaction of amino acids and related compounds with peroxide anions[226] and of the formation of peroxide anions in human blood cells;[222–229] in other cytological studies;[203–234] for chemiluminescent immunoassays[55] and for the development of sensors based on immobilised enzymes.[235,236]

Compounds **65** and **66** denoted by the abbreviations CLA and MCLA are analogues of luciferin **1** that are reused most frequently.



65



66

It has been noted (see for example, Refs 45 and 237) that MCLA is more effective than CLA for detecting oxidants formed during enzymic reactions this is due to a higher quantum yield in the former case and also to the fact that the maximum of its luminescence is shifted to the visible region to a greater extent (for CLA, λ_{max} is 45 nm[58] and for MCLA, it is 46 nm[45]).

It has been reported that the introduction of one of the analogues of *Cypridina* luciferin into rat heart tissue decreases the probability of fibrillation induced by ischemia and reperfusion.[238]

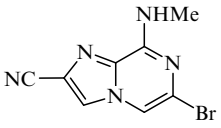
The main field of application of coelenterazine and its synthetic analogues is luminescent determination of calcium ions. As noted above, bioluminescent properties are inherent in the protein aequorin, in which the coelenterazine molecule acts as a prosthetic group. Bioluminescence is observed only in the presence of calcium ions,[1,6,17,49,50,148,239,240] while in the absence of these ions this protein is very stable.

The methods for investigation of the dynamics of calcium ions in living tissue is based on the formation of recombinant aequorin from coelenterazine or its analogues and the corresponding protein apoaequorin produced in the cells.[241,242] In a comparative study of the natural coelenterazine **2** and its synthetic analogues it has been found that the recombination of aequorin occurs most rapidly when natural coelenterazine is used.[243,244]

In the absence of protein, non-bound coelenterazine can be used as a luminescent probe for peroxide ions[245] and also for investigation of translation in cell-free systems.[246]

The main field of application of synthetic imidazopyrazines having no natural analogues is pharmacology. Some compounds of this class are capable of depressing the secretion of gastric juice; therefore they can be used as anti-ulcer drugs.[78,79,82,145,247–252] Among the imidazopyrazines mentioned in this review, the derivative **21y**, known under the code name SCH 32651, is the most active.[78,145,247–249]

Another type of pharmacological activity found for some representatives of this class of compound is the ability to relax smooth muscles.[71, 87, 135, 253–258] For example, it has been found that[71, 87] the imidazopyrazines **21k–m**, **49a–g** and some others possess more pronounced bronchospasmolytic properties than theophylline; as a rule, the activity of these compounds increases when bromine atoms are introduced in their molecules as substituents. 6-Bromo-8-methylaminoimidazo[1,2-*a*]pyrazine-2-carbonitrile **67** referred to as SCA 40 has been chosen for a systematic pharmacological assay.[254–258]



67

Cardiotonic properties (i.e. the ability to enhance systoles) have been discovered for derivatives containing methoxyphenyl and other aromatic substituents in the 2-position of the heterocyclic nucleus,[72 76, 77, 80, 259–261] for example, for the imidazopyrazines **21p–r**.

More complex compounds such as **55**,[140–142] **58**[144] as well as peneme[262, 263] and cepheme[264] antibiotics with imidazopyrazine substituents have been proposed as antibacterials.

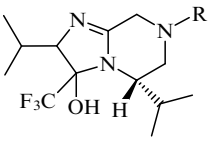
Some imidazo[1,2-*a*]pyrazine-2-carboxylic acids, imidazo[1,2-*a*]pyrazine-3-carboxylic acids[62, 64, 73, 84, 265] and the adenosine analogue **7**[37] exhibit anti-inflammatory activity. Some carboxyl-containing derivatives have been found to possess analgesic properties.

Imidazopyrazine analogues of nucleosides can prove to be effective antiviral preparations and immunomodulators.[36, 37, 266] For example, the compound **7** inhibited AIDS virus proliferation in T cells by 70%.[36]

It has been proposed to use the piperazino-derivatives **49h–k** as appetite-suppressing agents; as antidepressants; as antihypertensive, analgesic and antiarrhythmic preparations and in the fight against smoking.[33, 65, 267] 8-Piperazinoimidazo[1,2-*a*]pyrazine has exhibited hypoglycemic activity.[34, 268]

Ethyl 2,3,5,6,7,8-hexahydroimidazo[1,2-*a*]pyrazine-7-carboxylate has proved to be useful in the therapy of schizophrenia.[93]

The trifluoromethyl-substituted imidazo[1,2-*a*]pyrazines **68** have been found to be effective inhibitors of elastase and are considered as possible drugs for treatment of lung emphysema and related diseases.[269, 270]



68

R = 3,4-$(MeO)_2C_6H_3CH_2CH_2$, 2-indanyl, cyclooctyl.

Derivatives of oxoquinoline- and oxonaphthyridinecarboxylic acids containing imidazopyrazine substituents have been patented as preparations for the treatment of acute myocardial infarction, osteoporosis and tumours.[271]

There are only few examples, where synthetic imidazopyrazines have been used for other than pharmacological purposes. To the best of our knowledge, only a method for extraction of metal ions (Mo, Cr, Pb, Au, Ag, Pt, U, *etc.*) using the compound **36**[108] has been patented and materials for colour photography based on 5-hydroxyimidazo[1,2-*a*]pyrazines have been developed.[272, 273]

VII. Conclusion

Our analysis of the published data indicates that considerable progress has been achieved during the four decades of studies dealing with imidazo[1,2-*a*]pyrazines.

A number of methods for the synthesis of this class of compound have been developed. These methods permit preparation of products with different degrees of saturation of the imidazopyrazine nucleus and with side substituents of various natures. The approach based on the construction of the imidazole ring when the pyrazine fragment is already present in the molecule is used most frequently. Among the reagents used for these purpose, the best results have been generally achieved when pyrazines have been involved in condensation with α-halocarbonyl compounds. Glyoxals proved to be indispensable in the synthesis of natural luciferins and model compounds.

The synthesis of 'azacyclols' presented a separate task. It was accomplished using reagents and procedures adapted from peptide chemistry. This task was even more complicated due to the presence of chiral centres in the amino-acid residues — structural fragments of 'azacyclols' – and to the lability of the C(8a)OH group.

The current views on reactions of imidazopyrazines are mostly based on the data accumulated in the synthesis of new compounds of this class by introduction of side substituents into the heterocyclic ring and their subsequent modification. Systematic studies on the reactivity of imidazopyrazines have scarcely been carried out, except for the studies dealing with the structure of luciferins and the mechanism of their luminescence.

Studies of the spectroscopic properties and characteristic features of the electronic and spatial structures of some imidazo[1,2-*a*]pyrazines are not significant by themselves; as a rule, they only supplement synthetic studies by a standard set of analytical data for new compounds. Works, in which the attention is focused on these aspects (for example, studies on the tautomerism, sites of protonation and reactivity, confirmation of an unusual structure, *etc.*), are few in number.

About a quarter of all publications (including patents) on imidazopyrazines are devoted to their use or mention their possible applications (mostly in analytical chemistry, biochemistry and pharmacology).

Analysis of the published data makes it possible to distinguish some specific features in the development of this branch of the chemistry of heterocyclic compounds. As has been mentioned in the Introduction, the studiees devoted to the synthesis and studies of imidazopyrazines follow three absolutely separate lines of research:

(1) natural luciferins and their analogues;

(2) 'cyclols' and other derivatives of cyclic tripeptides;

(3) imidazopyrazines having no natural analogues.

The studies along the first line were actually initiated by the discovery of *Cypridina* luciferin and coelenterazine in living organisms. Although these are only two representatives of the vast class of imidazopyrazines, their properties are so interesting that publications dealing with the synthesis of their analogues and with the conclusive determination of the mechanism of their luminescence are still appearing in the literature. These studies occupy an important place among those dealing with the chemistry of imidazopyrazines.

The fate of the second line of research is somewhat unexpected and, from the author's viewpoint, difficult to explain. The first studies on the synthesis of 'azacyclols' were published in the early 70s, while the last ones appeared in the middle 80s. Despite the fact that these compounds are extremely interesting, this line is at a deadlock. Its development stopped about ten years ago and did not result even in recommendations on practical applications of azacyclols. According to the personal viewpoint of the author, development of more general and convenient methods for the synthesis of these compounds (including, for example, fluorinated derivatives) and appropriate pharmacological assays would not

only fill the gap in the purely practical aspect but also markedly contribute to peptide chemistry. The possibility of preparing other imidazopyrazine analogues of cyclic tripeptides directly from amino acids also deserves more attention.

As regards the chemistry of synthetic imidazopyrazines having no natural analogues, its development follows the traditional route for the majority of classes of organic compounds. Since many of the compounds synthesised exhibited valuable pharmacological properties, the search for new derivatives of this type is being carried out. Although it seems that pharmacology does not encompass all the possible applications of these compounds, other practical aspects are scantily presented in the scientific literature.

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