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BENZAZETINES AND THEIR DERIVATIVES (REVIEW)

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Published information on methods for the production of benzazetines and their dehydro derivatives (benzazetes) and their chemical transformations is reviewed and analyzed. It was noted that benzazetines with an unsubstituted NH group are unstable and their stable representatives have only became accessible in recent years. The tendency of benzazetines to undergo opening of the four-membered heterocycle and isomerization processes was demonstrated. The wide-ranging synthetic possibilities of benzazetines and benzazetes are indicated.

Keywords: benzazetinones, benzazetines, benzazetes, benzotriazines, heterocyclization, isomerization, thermolysis, photolysis, cycloaddition.

In the series of nitrogen-containing heterocyclic compounds benzazetines – 7-azabicyclo[4.2.0]octa-1,3,5-trienes – form a small and little investigated group, due to the instability of a series of their derivatives and also the fairly complicated methods for the synthesis of most of these compounds. They became known about 40 years ago, when they were first recorded as reactive intermediates in the photolysis of 3-phenylbenzo-1,2,3-triazine and its 4-oxo derivative [1, 2]. Later on, methods were developed for their synthesis from sultams, anthranilium salts, and other compounds capable of eliminating N_2, SO_2, or other small molecules during thermolysis, UV irradiation, or the action of chemical reagents. As a rule unstable benzazetines containing a substituent at the nitrogen atom of the heterocycle were obtained in all the described cases. Their N-unsubstituted analogs remained unobtainable until recently. All this held up investigation of the chemistry of benzazetines and prevented determination of their possible practical applications. It should be noted that azetidines not containing a benzene ring, first obtained at the end of the nineteenth century [3], are being studied vigorously due primarily to their high biological activity. The four-membered heterocycle in such compounds is a fragment of the molecules of antibiotics of the penicillin and cephalosporin group [4-6]. This makes it possible to suppose that benzazetines may also exhibit biological activity.

The few earlier works on the synthesis of benzazetines were summarized in the monograph [7] and to some extent in two reviews [8, 9]. In recent years new reports have appeared on the production of compounds of this group, and in particular a fundamentally new convenient approach to the synthesis of stable N-unsubstituted benzazetine systems based on readily available azolyl derivatives of nitrohalobutadienes [10, 11]. Some chemical characteristics of the synthesized benzazetines, among which there are compounds with antitumor activity [12] and substances acting as resists in the plasmochemical etching of silicon and its dioxide, were studied [13].

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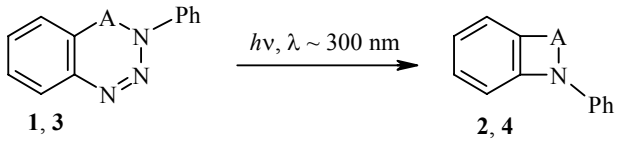
In the present review data on these compounds and also on their dehydro derivatives, benzazetes, published up to 2006 have been classified and analyzed in order to encourage the development of new methods for the production of benzazetines, study of their transformations, and the discovery of useful properties.

1. METHODS OF SYNTHESIS OF BENZAZETINES

Most methods for the synthesis of benzazetines are based on the elimination of N_2, SO_2, NH_3, H_2O, C_2H_4, CO, CO_2, or amines from the molecules of the initial substances by the action of radiation, heat, or chemical reagents and also on the isomerization of the compounds with rearrangement of the carbon skeleton. The two reactions can be combined into a single process leading to the formation of the benzazetine system.

1.1. Synthesis of Benzazetines by Photolysis of Derivatives of Benzo-1,2,3-triazines

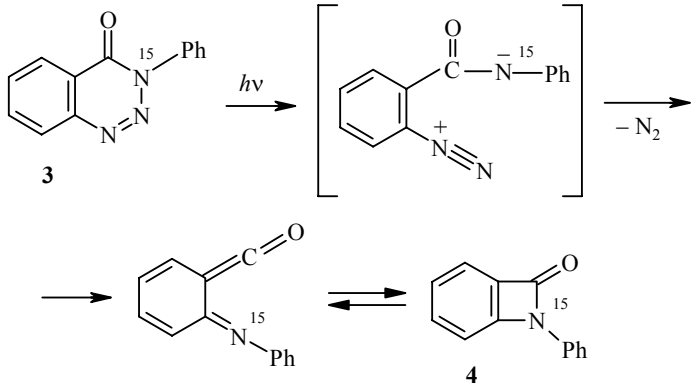
The formation of the benzazetine system was first detected by Burgess and coworkers during the UV irradiation of phenylbenzo-1,2,3-triazine derivatives in benzene. N-Phenylbenzazetine (**2**) was obtained with a yield of 50% from 3-phenyl-4H-benzo-1,2,3-triazine (**1**) [2], while N-phenylbenzazetinone (**4**) was obtained with a high yield from the 4-oxo derivative **3** [1].



1, **3** **2**, **4**

1, **2** A = CH_2, **3**, **4** A = CO

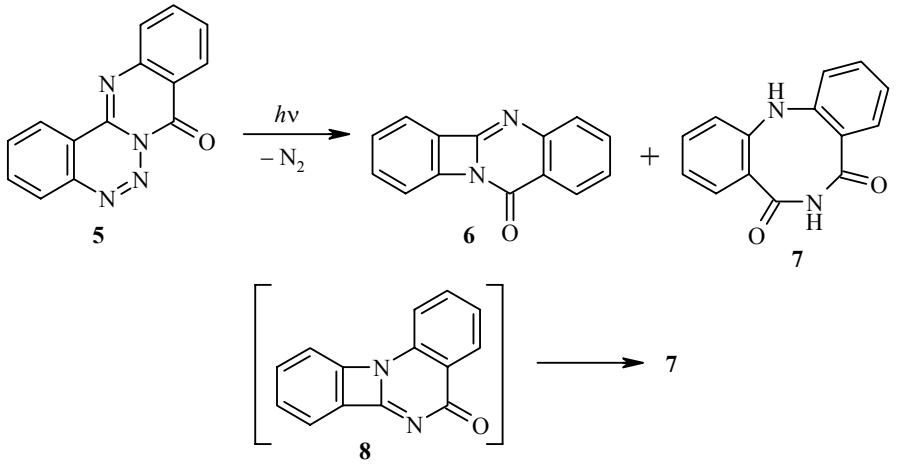
A mechanism for the formation of benzazetinone **4** involving the initial cleavage of the $N_{(2)}$–$N_{(3)}$ bond followed by elimination of a molecule of nitrogen was subsequently proposed on the basis of the results from a detailed investigation of the photolysis of the isotope-labeled compound **3** by mass spectrometry [14, 15].



3 **4**

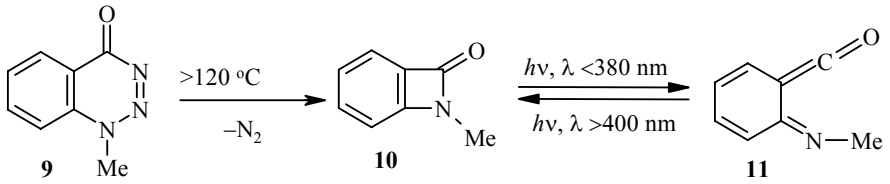
More complicated condensed molecules containing the bicyclic fragment of benzotriazine are also capable of eliminating N_2 during irradiation with the formation of compounds containing a benzazetine structure. In particular, the products from photolysis of 8-oxo-8H-quinazolino[3,2-*c*]-1,2,3-benzotriazine (**5**) in

tetrahydrofuran and dichloromethane are 11-oxo-11H-benz[3,4]azeto[2,1-*b*]quinazoline (**6**) (38%) and diphenylamine-2,2′-dicarboximide **7** (yield 47%) [16]. Compound **7** is probably formed from the intermediate 5-oxo-5H-benz[3,4]azeto[1,2-*a*]quinazoline (**8**), isomeric with the product **6**.

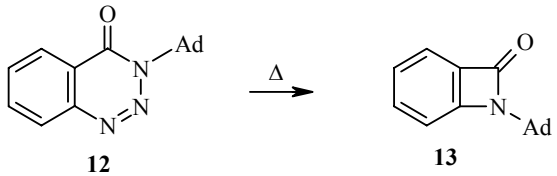


1.2. Synthesis of Benzazetines by Thermolysis of Derivatives of Benzo-1,2,3-triazines or by the Action of Chemical Reagents on them

Photolysis of the $N_{(2)}$–$N_{(3)}$ bond of the triazine ring with the elimination of a nitrogen molecule is not the only possible method since 1,2,3-benzotriazin-4-ones substituted at the $N_{(1)}$ or $N_{(3)}$ atoms are also transformed into the corresponding benzazetinones during thermal decomposition [17, 18]. Thus, the pyrolysis of 1-methyl-1,2,3-benzotriazin-4(1H)-one (**9**) at a temperature above 120°C led to the formation of the extremely labile N-methylbenzazetinone (**10**), which was stabilized in a matrix of solid argon at -258°C. Under the influence of UV light (λ < 380 nm) the product **10** partly isomerized to the iminoketene **11**, the reverse transformation of which to the azetinone **10** occurred at a longer wavelength (λ > 400 nm) [17].

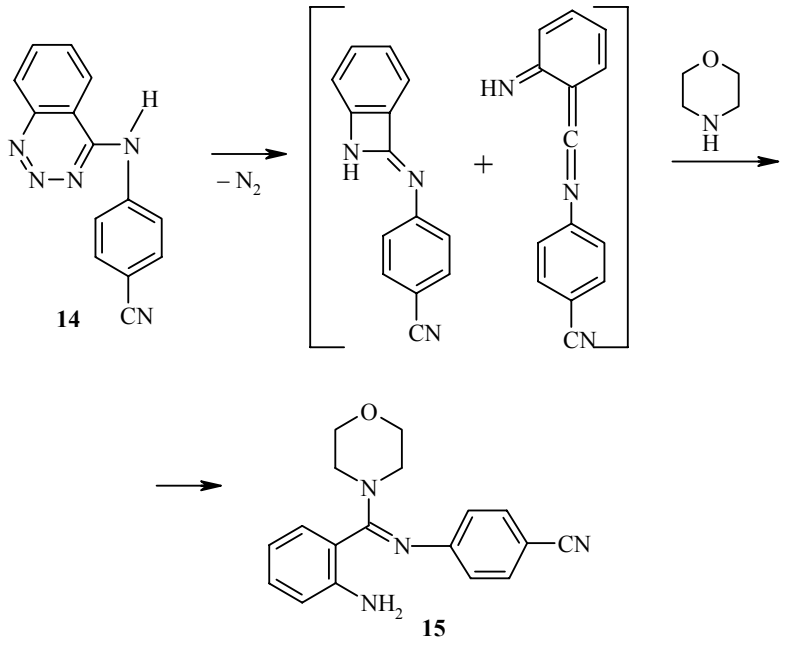


Similarly, N-(1-adamantyl)benzazetinone (**13**) was obtained with a yield of 30% during the pyrolysis of 3-(1-adamantyl)-1,2,3-benzotriazin-4(3H)-one (**12**) [18].



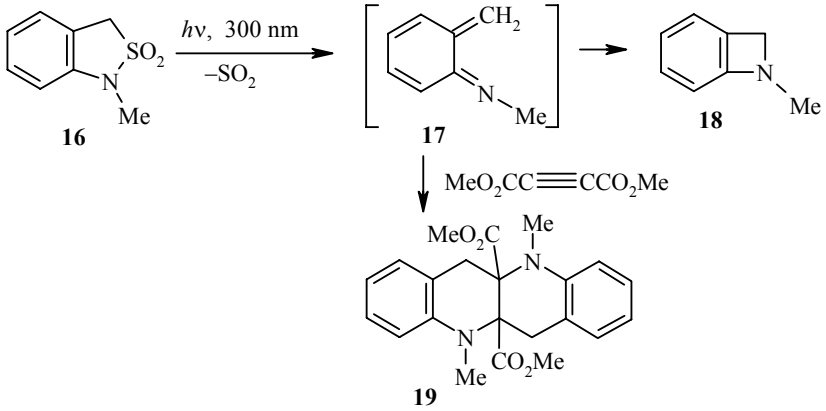
Here and subsequently Ad = 1-adamantyl

The thermolysis of substituted benzotriazines in various secondary amines was investigated in detail. The main products of this reaction were substituted benzamidines, formed as a result of the reaction of reactive intermediates (benzazetines and imines) with the amines [19-21]. Thus, the formation of the amidine **15** according to the scheme below is possible during the thermolysis of 4-(4-cyanophenylamino)-1,2,3-benzotriazine (**14**) in morpholine [19].



1.3. Synthesis of Benzazetines from Sultams

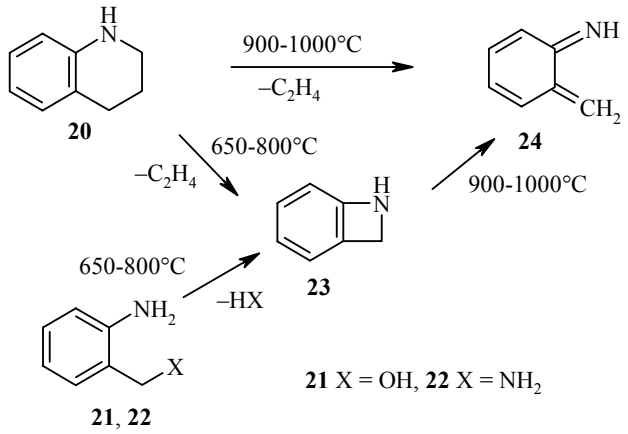
The production of benzazetine structures from sultams seems quite promising in practical respects. It was shown [22] that sulfur dioxide is eliminated during the photolysis of 1-methyl-2,1-benzothiazoline 2,2-dioxide (benzosultam **16**), and N-methylbenzazetine (**18**) is formed with a yield of 62% through the intermediate imine aza-*ortho*-xylylene **17**. The presence of the imine **17** in the reaction mixture was confirmed by the formation of its adducts with dienophiles. Thus, the tetracyclic derivative **19** was isolated during the photolysis of the sultam **16** in the presence of dimethyl acetylenedicarboxylate.



The work in [23] was concerned with investigation of the products from flash-vacuum thermolysis of various substituted benzosultams by UV photoelectron spectroscopy. It was shown that the formation of some products of this reaction (aldimines) is possible as a result both of migration of a hydrogen atom in the initially formed aza-*ortho*-xylylenes and of the participation of the corresponding benzazetines. Reviews have been devoted to the generation of aza-*ortho*-xylylenes and their reactions [8, 9].

1.4. Formation of the Benzazetine System by Flash-Vacuum Pyrolysis

Systems with the benzazetine bicycle are formed during the flash vacuum pyrolysis of certain *ortho*-heterosubstituted benzenes and tetrahydroquinoline. This method is of no use in practical respects but is interesting in that it leads to benzazetines with an unsubstituted NH group. The products from flash-vacuum pyrolysis of 1,2,3,4-tetrahydroquinoline (**20**), *o*-aminobenzyl alcohol (**21**), and *o*-aminobenzylamine (**22**) over a wide range of temperature were investigated by photoelectron spectroscopy. The reactions took place as a result of elimination of C_2H_4, NH_3, and H_2O molecules respectively. Here it was found that the benzazetine (**23**) is formed at 650-800°C while the product at higher temperature is 6-methylene-2,4-cyclohexadiene-1-imine (**24**) [24, 25].

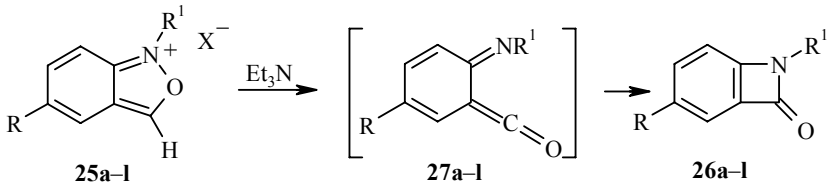


Subsequent more detailed investigations of flash-vacuum pyrolysis and low-temperature photolysis in a matrix of 2-(diazomethyl)phenylamine, 1-azido-2-methylbenzene (2-tolyl azide), *o*-aminobenzyl alcohol, and 2-indolinone by IR and UV spectroscopy in conjunction with *ab initio* quantum-chemical calculations showed that these reactions take place in a more complicated manner. It was established in particular that the imine **24** represents a mixture of *E*- and *Z*-isomers while the isomeric benzazetine **23** is not formed in all cases [26, 27].

1.5. Synthesis of Benzazetine Derivatives from Anthranilium Salts

The method for the production of N-substituted benzazetines based on anthranilium salts **25a-d** has been developed in considerable detail. When the anthranilium salts are treated with triethylamine (dichloromethane, 25°C) the desired compounds are formed with yields of 73-97% [28]. It is interesting to note that the products differ substantially in their stability at room temperature: N-*tert*-butylbenzazetinone **26d** is a stable compound, the methyl- and ethyl-substituted benzazetinones **26a**,**b** decompose after 1 h, and their homolog **26c** (R = *i*-Pr) is stable for 24 h.

A possible mechanism was proposed for the reaction, involving removal of a proton from the $C_{(3)}$ atom of the initial compound **25** with ring cleavage and the formation of the intermediate iminoketene derivative **27**, which then undergoes cyclization to the benzazetinone **26** [28].



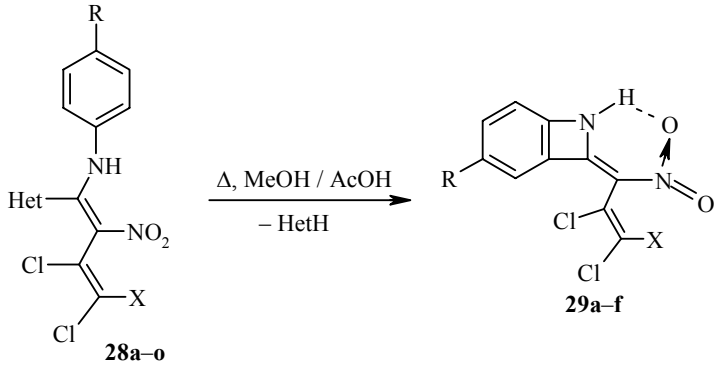
25a–l **27a–l** **26a–l**

25–27 a–g X = ClO_4, **a–e** R = H, **a** R^1 = Me, **b** R^1 = Et, **c** R^1 = *i*-Pr, **d** R^1 = *t*-Bu, **e** R^1 = Ad;
f, **g** R = Br, **f** R^1 = *t*-Bu, **g** R^1 = Ad; **h–j** X = BF_4, R = H, **h** R^1 = Me, **i** R^1 = Et, **j** R^1 = *i*-Pr;
k X = CF_3SO_3, R = H, R^1 = Me, **l** X = FSO_3, R = H, R^1 = Et

This reaction was subsequently extended to the anthranilium salts **25e-l**, where the structure of the synthesized benzazetinones **26e-l** was confirmed reliably for N-(1-adamantyl)benzazetinone **26g** by X-ray crystallographic analysis [29].

1.6. Synthesis of Functionally Substituted Benzazetines Based on Azolyl Derivatives of Nitrohalobutadienes

Recently the authors of this review found a convenient method for the production of benzazetines with an unsubstituted amino group from readily available 1-arylamino-1-azolyl-2-nitro-3,4,4-trihalogenated butadienes **28a-o**. Thus, when the latter are heated in proton-donating solvents (methanol, acetic acid, 55-60°C, 10 h) the corresponding azole is eliminated, and 2-(1-nitrohalopropenylidene)-4-R-benzazetines **29a-f** are formed [10, 11, 30-32].



28a–o **29a–f**

28 a-g Het = 1,2,3-benzotriazol-1-yl, **h–m** Het = 3,5-dimethylpyrazol-1-yl,
n, **o** Het = 1,2,4-triazol-1-yl; **28 a–d**, **h–j**, **29a–d** X = Cl, **28e–g**, **k–o**, **29e**, **f** X = Br;
28a, **29a** R = OBu; **28b**,**e**,**h**,**k**,**n**, **29b**,**e** R = OEt; **28c**,**f**,**i**,**l**, **29c**,**f** R = OMe,
28d,**g**,**j**,**m**,**o**, **29d** R = Me

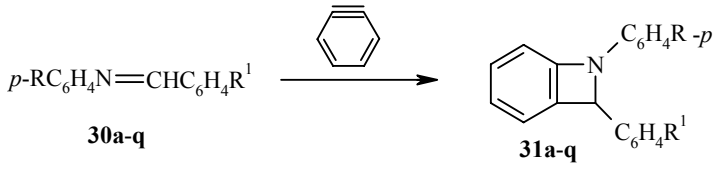
When the reaction is carried out in any of the above-mentioned solvents the yields of the alkoxy-substituted products **29a-c**,**e**,**f** amount to 70-91%. The yield of the methyl-substituted benzazetine **29d** depends on the choice of solvent: with acetic acid it amounts to 60%, in methanol not more than 25%, and there is considerable resin formation. The reaction does not take place in ether, while in benzene the reaction mixture is resinified.

It was established that the reaction is not significantly affected by the nature of the azolyl substituent in the initial compounds **28a-o**. On the other hand the nature of the substitution in the ArNH fragment is extremely important; in cases where this fragment was aniline, *p*- and *m*-bromoanilines, *m*-toluidine, *p*-aminobenzoic acid, and 2,4-diaminotoluene attempts to obtain the benzazetines were unsuccessful. Substitution of the terminal halogen atom by an amine group led to resinification and the formation of a complex mixture of substances.

By ^{1}H and ^{13}C NMR spectroscopy and also by TLC it was shown that the benzazetines **29a-f** exist in one isomeric form and probably have the *Z*-configuration for the diene substituent; in this case the molecule is stabilized as a result of the formation of an intramolecular hydrogen bond between the nitro and amino groups with delocalization of the π-electrons and the formation of a six-membered ring [33], as shown in the formula **29** presented above.

1.7. Synthesis of Benzazetines by [2+2] Cycloaddition

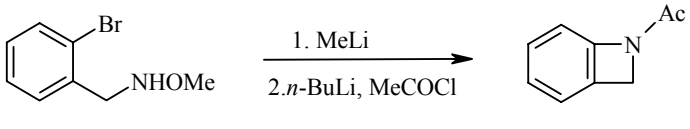
The regioselective synthesis of 1,2-diarylbenzazetines **31a-q** was recently realized by [2+2] cycloaddition of dehydrobenzene, generated *in situ*, to the azomethines **30a-q** [34]. The yields of these products amounted to 55-68%.



30, **31 a-e** R = H, **a** R^1 = H, **b** R^1 = 4-Me, **c** R^1 = 4-OMe, **d** R^1 = 4-OEt, **e** R^1 = 4-NO_2;
f–k R = OMe, **f** R^1 = H, **g** R = Me, **h** R^1 = OMe, **i** R^1 = OEt, **j** R^1 = 4-Cl, **k** R^1 = NO_2;
l–q R = Cl, **l** R^1 = H, **m** R^1 = 4-Me, **n** R^1 = 4-OMe, **o** R^1 = 4-OEt, **p** R^1 = 4-Cl,
q R^1 = 3-NO_2

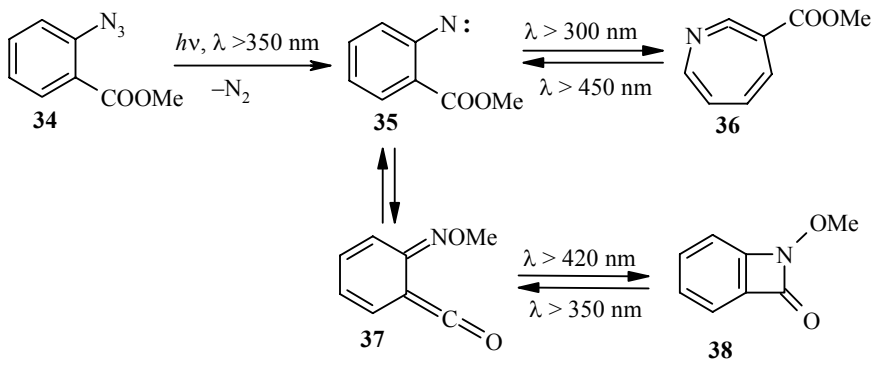
1.8. Other Methods for the Synthesis of Benzazetines

N-Acetylbenzazetine (**33**) was obtained with a yield of 21% from N-(*o*-bromobenzyl)methoxyamine (**32**). The key stage of the reaction is double lithiation of the initial amine **32**, leading to the (*o*-lithiophenyl)alkyllithiomethoxyamide, which forms the benzazetine **33** as a result of cyclization. The structure of the latter was confirmed by X-ray crystallographic analysis [35].

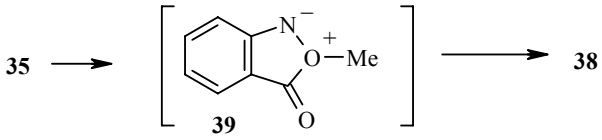


32 **33**

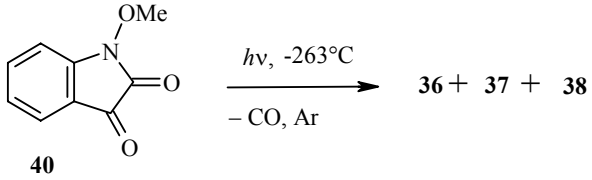
By analysis of the UV spectra it was shown that at least five main compounds capable of interconversion of the products are formed during irradiation of 2-(methoxycarbonyl)phenyl azide **34** (λ > 350 nm, argon, -263°C): Nitrene **35**, aza-1,2,4,6-cycloheptatetraene **36**, two geometric isomers of carbonyl-(methoxyimino)benzene **37**, and benzazetinone **38** [36].



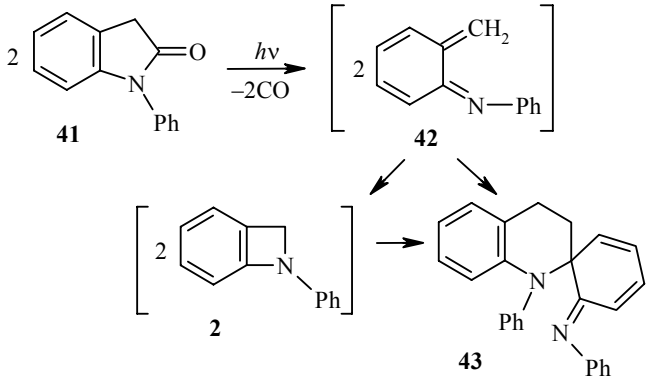
The intermediate isomers **37** are probably formed on account of 1,4-migration of the methoxy group in the nitrene **35**, leading to the appearance of the oxonium imide **39** – the precursor of the benzazetinone **38**.



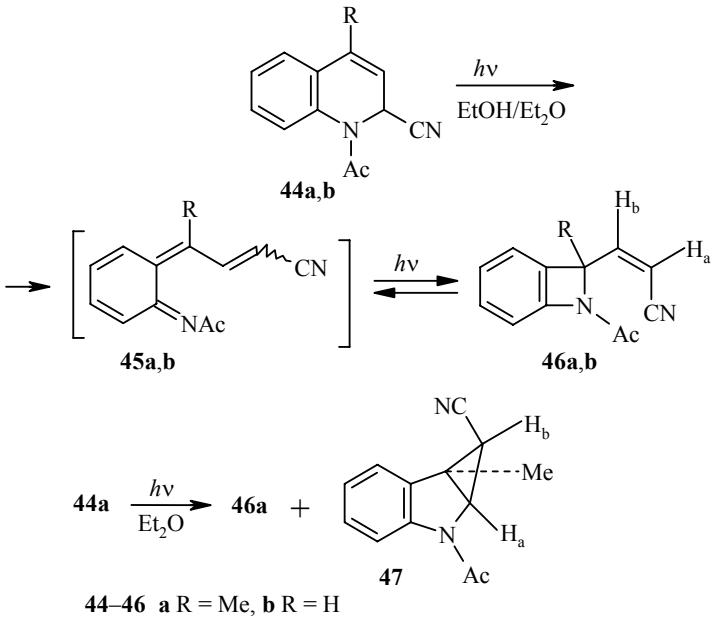
In the same work the formation of the products **36-38** was detected during the decarboxylation of N-methoxyisatin **40** under analogous conditions.



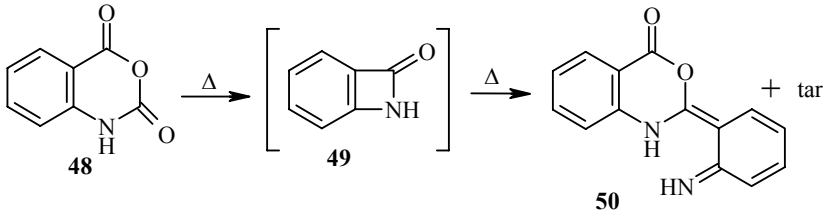
The photodecarbonylation of N-phenoxyindole **41** in hexane leads through the intermediate anil **42** and azetine **2** to the spiro compound **43** [37]. Small amounts of compound **2** were detected in the reaction mixture by TLC, and in a separate experiment with an authentic sample it was shown that it is transformed very easily into the product **43** during irradiation.



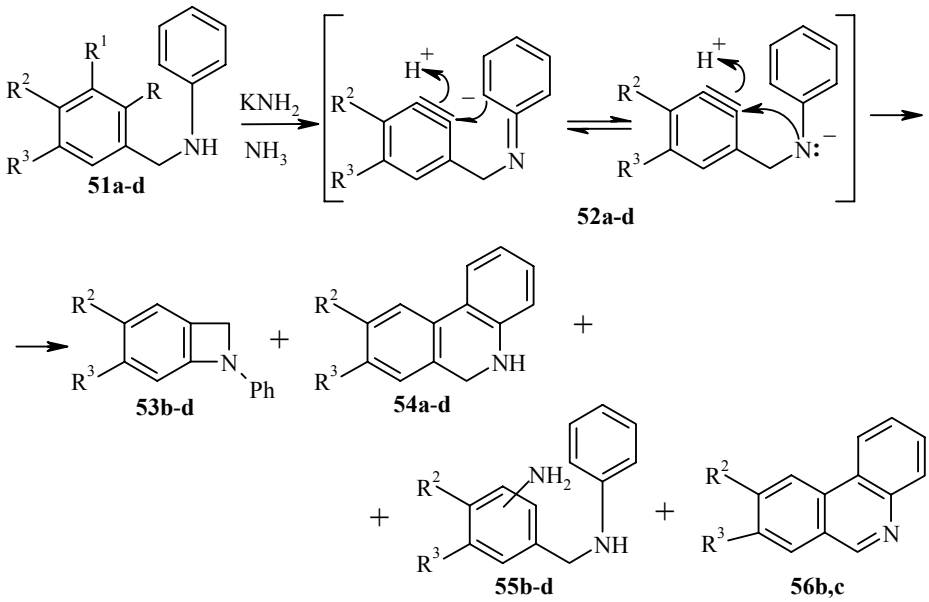
During the irradiation of 1-acetyl-2-cyano-1,2-dihydroquinolines **44a**,**b** in ether or ethanol (a high-pressure lamp, 350 W) their isomerization leading to the formation of N-acetylbenzazetines **46a**,**b**, presumably through the intermediates **45a**,**b**, is observed [38]. Thus, the quinoline **44a** is transformed into compounds **46a** and **47**, the yields of which depend on the duration of the process and on the solvent: When the reaction was carried out in ether for 5 h the yields of the products **46a** and **47** were 30 and 54% respectively; during brief irradiation (~1 h) compound **46a** was the main product, and after irradiation for 10 h it disappeared completely [38], but the amount of the product **47** and the polymer increased. It was shown according to data from ^{1}H NMR that compound **46a** was in the *cis* form.



It was established by spectroscopic methods that the benzazetinone **49** is formed as intermediate during the thermolysis of isatoic anhydride **48**. It proved extremely unstable under the reaction conditions and was quickly transformed into the dimer **50** and resinous products [39].



The authors of [40] studied the possibility of synthesizing N-substituted benzazetines by treating N-substituted benzylamines with KNH_2 in liquid ammonia. It was shown that mixtures of products **53**-**55** with compositions determined by the nature of the substituents in the benzyl fragment (R^2, R^3) are formed in the case of 1-phenylbenzylamines **51a**-**d** presumably through the intermediate arynes **52a**-**d**. The corresponding benzazetine **53a** is not formed from the unsubstituted amine **51a**, where the main product is dihydrophenanthridine **54a** (yield >90%).



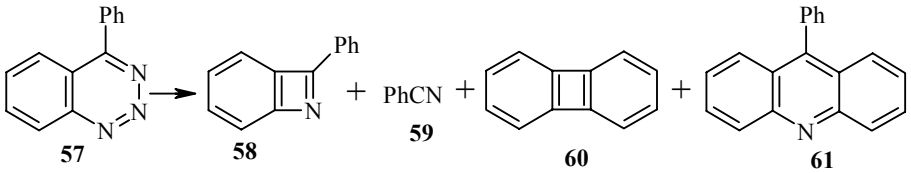
51 a R = Cl, R^1 = H, **b** R = Br, R^1 = H; **c**, **d** R = H, R^1 = Br; **51**–**56 a** $R^2 = R^3$ = H, **b** $R^2 = R^3 = OCH_2O$, **c** $R^2 = R^3$ = OMe, **d** R^2 = OMe, R^3 = H

The respective benzazetines **53b** (28%), **53c** (6%), and **53d** (1%) were obtained from the amines **51b-d**, and the phenanthridines **56b**,**d** were also isolated together with compounds **53b**,**c**. Careful study of the composition of the reaction mixtures (in order to avoid further transformations of the labile reaction products the reactions were carried out under nitrogen, and the obtained mixtures were treated with acetic anhydride for subsequent isolation of the stable acetylation products) showed that dihydrophenanthridines **54b-d** (yields ~13-30%) and benzylanilines **55b-d** (53-84%) are also formed from compounds **51b-d**. The isolated phenanthridines **56b**,**c** are the products from the oxidation of their unstable dihydro derivatives **54b**,**c** in air.

It should be noted that it was not possible to obtain 1-alkylbenzazetines (alkyl: Et, CH_2Ph, $CH_2C_6H_4Me$-*p*) in this work; under the indicated conditions the initial N-alkylbenzylamines were converted either into the products from substitution of the halogen atom by a NH_2 group (type **55**) or into imines – the products from elimination of hydrogen in the $NHCH_2$ fragment.

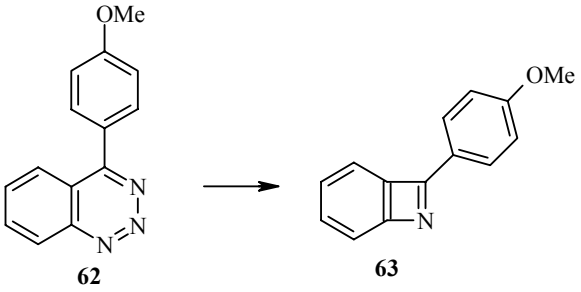
2. METHODS OF SYNTHESIS OF BENZAZETES

The dihydro derivatives of benzazetines, benzazetes, that have been less accessible until recently are produced by the pyrolysis of substituted triazines. Thus, the first example of benzazetes, 2-phenylbenzazete **58**, was obtained in 1973 during the gas-phase pyrolysis ($t \leq 400$°C) of 4-phenyl-1,2,3-triazine **57** [41]. Under optimum conditions (420-450°C, pressure 10^{-3} mm Hg) flash-vacuum pyrolysis of the triazine **57** also led to the formation of the azete **58** with a yield of 60%. In addition, benzonitrile **59**, biphenylene **60** (the product from dimerization of the intermediate dehydrobenzene), and 9-phenylacridine **61** were also found in the reaction products [42]. The azete **58** is an extremely unstable readily dimerizing compound that is only stable at temperatures below -40°C [42, 43]. The properties of the azete **58** are described in greater detail in section 3.3.



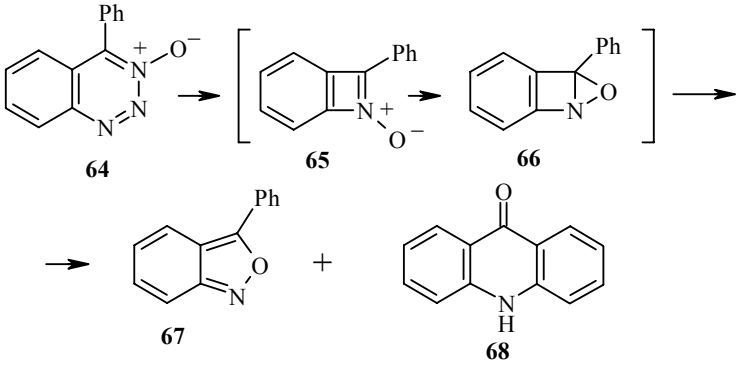
57 **58** **59** **60** **61**

The more stable 2-(*p*-methoxyphenyl)benzazete **63** was obtained with a yield of 21% from 4-(methoxyphenyl)-1,2,3-benzotriazine **62** [42].



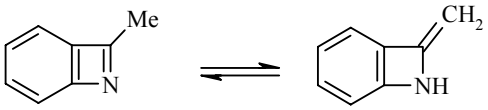
62 **63**

The pyrolysis of 6-chloro-4-phenyl-1,2,3-benzotriazine gave a low yield (6%) of the dimer of 4-chloro-2-phenylbenzazete [43]. 3-Phenyl-2,1-benzisoxazole **67** (yield 25%) and acridone **68** (yield 25%) were obtained from 4-phenyl-1,2,3-benzotriazine 3-oxide **64**, presumably through 2-phenylbenzazete 1-oxide **65** and its tricyclic isomer **66** [43].



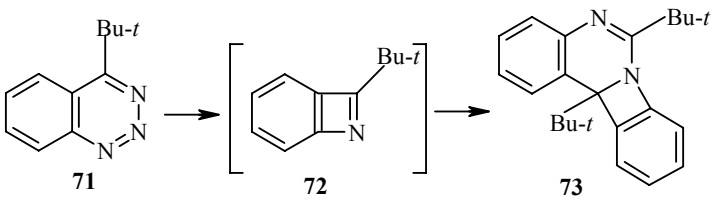
64 **65** **66** **67** **68**

It should be mentioned that attempts to obtain benzazetes with substituents other than aryl groups at position 2 were unsuccessful. Thus, the pyrolysis of 4-methyl-1,2,3-benzotriazine led to the formation of a complex mixture of products, but it was not possible to obtain convincing evidence for the presence of 2-methylbenzazete **69** in the reaction mixture [44]. It can be supposed that it quickly isomerizes on account of the mobility of the methyl hydrogen atoms to the less stable tautomer **70**, which readily polymerizes.



69 **70**

During the pyrolysis of 4-*tert*-butyl-1,2,3-benzotriazine **71** instead of (2-*tert*-butyl)benzazete **72** its dimer **73** was found among the reaction products, demonstrating the ease with which the azete dimerizes [44].



Earlier data on the production and chemistry of benzazetes were presented in the review [45].

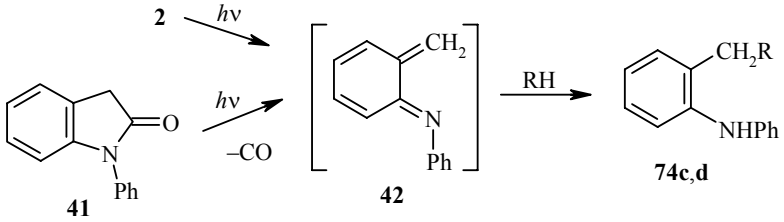
3. CHEMICAL TRANSFORMATIONS OF BENZAZETINES AND BENZAZETES

3.1. Reactions of Benzazetines

The above-mentioned instability of benzazetines is due to their high reactivity, which was first demonstrated for the case of N-phenylbenzazetine **2**. During its reaction with aniline (benzene, 30-80°C) a high yield of the ring opening product **74a** was obtained. When the azetine **2** was boiled with acetic acid or sodium acetate in benzene compound **74b** was formed [2].

74 a R = NHPh, **b** R = OAc

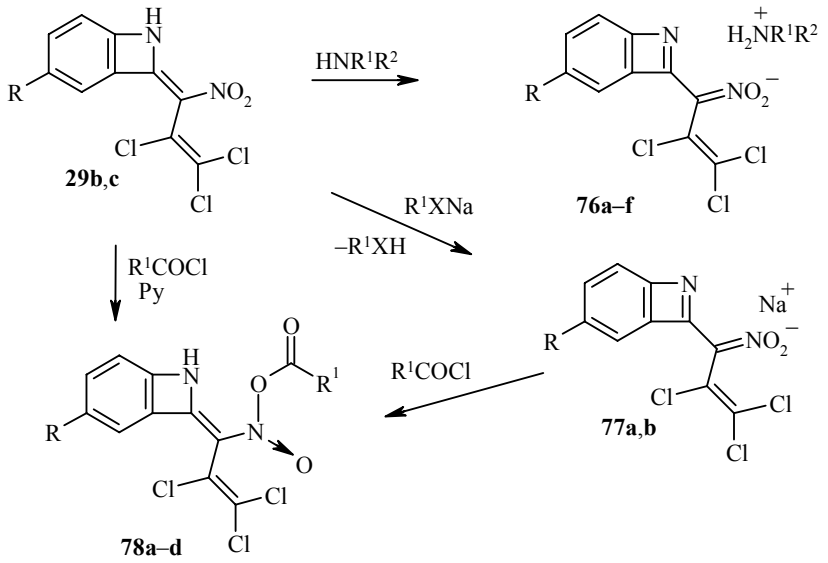
Analogous products **74c**,**d** were obtained during the irradiation of compound **2** in the presence of aniline or piperidine respectively. In [46] identical compounds were obtained during the photochemical decarbonylation of N-phenylindole **41** in the presence of amines. These results indicate that in both cases ring opening in the initial heterocyclic compound leads to the formation of the intermediate anil **42**, reaction of which with the RH reagent leads to the products **74**.



74 c R = NHPh, **d** R = $N(CH_2)_5$

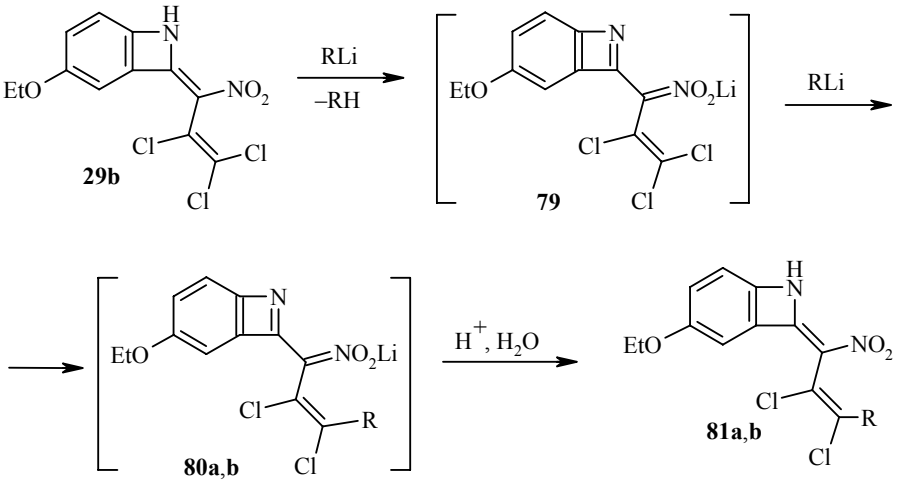
It was established that the action of *tert*-butylamine, diethylamine, piperidine, and sodium alcoholates and thiolates RXNa (X = O, R = Me, Et; X = S, R = Ph, CH_2Ph) on the azetines **29b**,**c** leads to the transformation of the benzazetine system into a benzazete system and of the nitro group into the *aci* form with the formation of the respective salts of nitronic acids **76a-f** and **77a**,**b** with yields of 70-80%. Quantum-chemical calculations for the reaction of benzazetine **29b** with diethylamine confirmed that the formation of the nitronic salt **76b** is the thermodynamically most favorable direction of the process [47]. In the reaction of the azetines **29b**,**c** with benzoyl and chloracetyl chlorides in the presence of pyridine the corresponding mixed anhydrides of

nitronic acids **78a-d** were obtained with yields of 60-65%. These anhydrides were also synthesized by the action of chloracetyl chloride and benzoyl chloride on the corresponding sodium salts **77a**,**b**, providing further evidence for the structure of the latter [30].



29 b R = OEt, **c** R = OMe; **76 a–c** R = OEt, **d–f** R = OMe, **a**, **d** R^1 = H, R^2 = Bu-*t*, **b**, **c** $R^1 = R^2$ = Et, **c**, **f** $R^1+R^2 = (CH_2)_5$; **77 a** R = OEt, **b** R = OMe; **78 a**, **b** R = OEt, **c**, **d** R = OMe, **a**, **c** R^1 = Ph, **b**, **d** $R^1 = CH_2Cl$

The reaction of benzazetine **29b** with methyl- and phenyllithium was studied in ether at 20-25°C with the reagents in various ratios. If the **29b** : RLi ratio is 1 : 2, as in the case of the formation of the salts **76** and **77** the reaction takes place through a stage involving reversible transformation of the nitro group into the *aci* form and of the benzazetine ring into a benzazete ring and the initial formation of the lithium salt of the nitronic acid **79**. This is followed by substitution of the terminal chlorine, leading to the intermediate salts **80a**,**b**. During treatment of the reaction mixture with water or a weak solution of hydrochloric acid these salts are transformed into benzazetines **81a**,**b** with yields of 45 and 52% respectively [48].

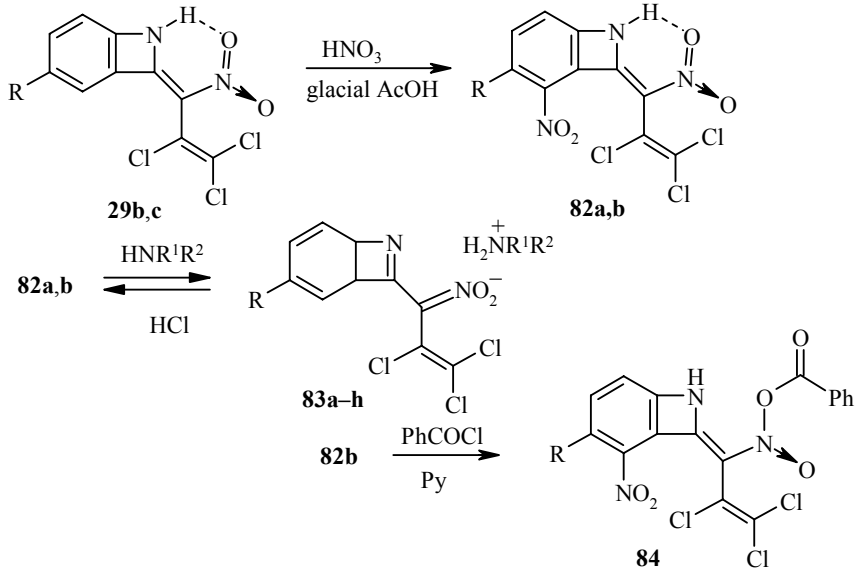


80, **81 a** R = Me, **b** R = Ph

In the case of a fivefold excess of phenyllithium a mixture of products from substitution of one, two, and three chlorine atoms in the azetine **29b** by phenyl groups is formed, while treatment of the azetine **29b** with a fivefold excess of methyllithium leads to the formation of a complex mixture of products and is accompanied by significant resin formation [48].

The nitration of the benzazetines **29b**,**c** with anhydrous nitric acid in glacial acetic acid at 10-15°C was studied. It was shown that the products from substitution at position 3 of the benzene ring – 3-nitro-substituted benzazetines **82a**,**b** respectively – are formed under these conditions with yields of 95-97% [49].

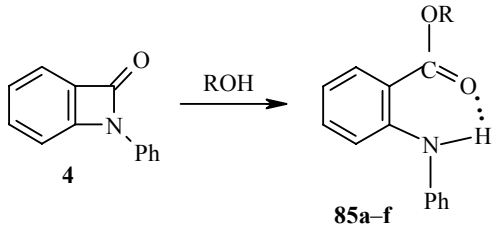
In the same work the synthesized azetines **82a**,**b** were reacted with amines (piperidine, morpholine, *tert*-butyl- and diethylamine). As in the case of compounds **29b**,**c**, the benzazetine system was transformed into a benzazete system while the nitro group was transformed into the *aci* form, leading to the formation of the salts of nitronic acids **83a-h** with yields of 79-97% [49]. In the reaction of the benzazetine **82b** with benzoyl chloride in the presence of pyridine the mixed anhydride (**84**) was obtained with a yield of 72% [49].



29 b R = OEt, **c** R = OMe; **82a**, **83a**–**d** R = OEt, **82b**, **83e**–**h** R = OMe, **83a**,**e** R^1 = H, R^2 = Bu-*t*, **b**, **f** $R^1 = R^2$ = Et, **c**, **g** $R^1+R^2 = (CH_2)_5$; **d**, **h** $R^1+R^2 = (CH_2)_2O(CH_2)_2$

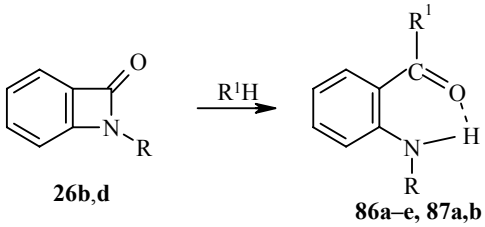
3.2. Chemical Transformations of Benzazetinones

The reactions of benzazetinones were first studied for the case of N-phenylazetinone **4**. During its reaction with alcohols (methyl, ethanol, isopropyl, and *tert*-butyl) and also with phenol and β-naphthol the reactions took place with opening of the four-membered ring and the formation of the corresponding esters **85a-f** with preparative yields [14, 15].



85 a R = Me, **b** R = Et, **c** R = Pr-*i*, **d** R = Bu-*t*, **e** R = Ph, **f** R = β-$C_{10}H_7$

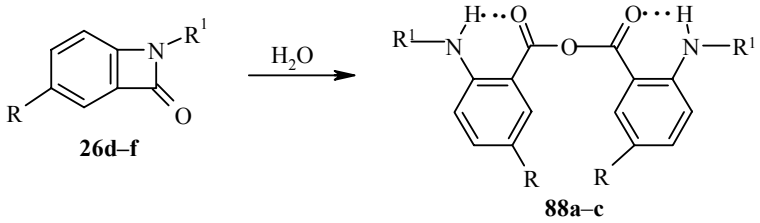
Later Olofson and coworkers [29, 50, 51] studied in detail the reaction of N-alkyl-substituted benzazetinones **26b**, **d** with various nucleophiles. From N-(*tert*-butyl)benzazetinone **26d** and alcohols the corresponding aromatic amino esters **86a-d** were obtained with yields of 74-95%. During treatment of the unstable N-ethylbenzazetinone **26b** with methanol the yield of the ester **86e** amounted to 61%. The reactions of the azetinone **26d** with diethylamine and pyrazole led to the amides **87a** (yield 87%) and **87b** (yield 85%) [29].



26b,**d** **86a–e, 87a,b**

86 a–d R = Bu-*t*, **a** R^1 = OMe, **b** R^1 = OEt, **c** R^1 = OPr-*i*, **d** R^1 = OBu-*t*;
e R = Et, R^1 = OMe; **87 a**,**b** R = Bu-*t*, **a** R^1 = NEt_2, **b** R^1 = 1-pyrazolyl

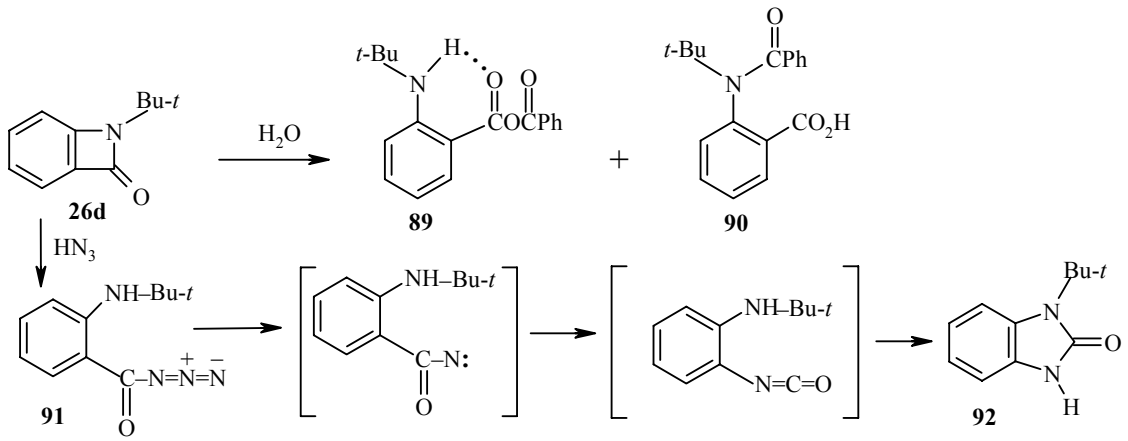
The benzazetinones **26d-f** react with water in an unusual way. The reaction also takes place with opening of the heterocycle but is accompanied by dimerization, resulting in the formation of the corresponding anhydrides. Thus, N-(*tert*-butyl)anthranilic anhydride **88a** was obtained with a 75% yield when a solution of compound **26d** in acetonitrile was treated with water. Under analogous conditions the azetinones **26e**,**f** form the anhydrides **88b** and **88c** with yields of 81 and 85% respectively [29].



26d–f **88a–c**

88 a R = H, R^1= Bu-*t*, **b** R = H, R^1 = 1-adamantyl, **c** R = Br, R^1 = Bu-*t*

The reaction of the azetinone **26d** with benzoic acid leads to the unstable mixed anhydride **89**, which is converted into the amide **90** when boiled in acetonitrile. Treatment of the azetinone **26d** with an ether solution of HN_3 gives the unstable acyl azide **91**, which undergoes rearrangement to the benzimidazolone **92** when heated [29].



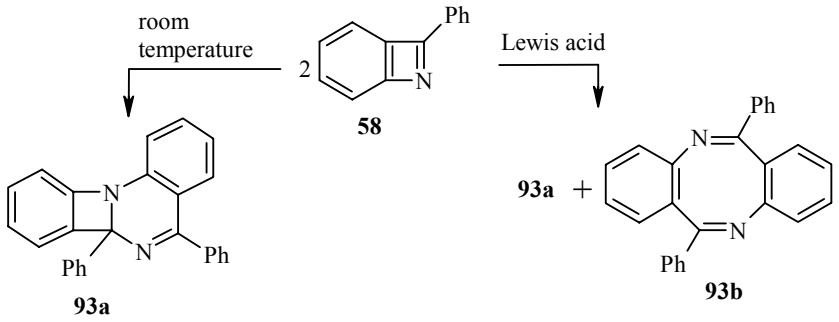
26d **89** **90** **91** **92**

3.3. Syntheses Based on Benzazetes

The transformations of benzazetes have only been described in the literature in relative detail in the case of 2-phenylbenzazete **58**.

It has already been mentioned above (see section 2) that the azete **58**, which is fairly stable only at -80°C, is formed with a yield of ~60% during the gas-phase pyrolysis of triazine **57**. At a higher temperature it is transformed into the dimer **93a** [41], the structure of which was established by X-ray crystallographic analysis [42]. The monomer **58** can be fixed in the form of products produced during the addition of nucleophiles or conjugated dienes to the cooled pyrolyzate (−40°C and below). Thus, if a 2N solution of sulfuric acid in tetrahydrofuran is added to the cooled pyrolyzate at −78°C *o*-aminobenzophenone is formed with a yield of 64% [43]. Treatment of the pyrolyzate at the same temperature with a solution of phenylhydrazine in dichloromethane leads to *o*-aminobenzophenone phenylhydrazone [41, 43].

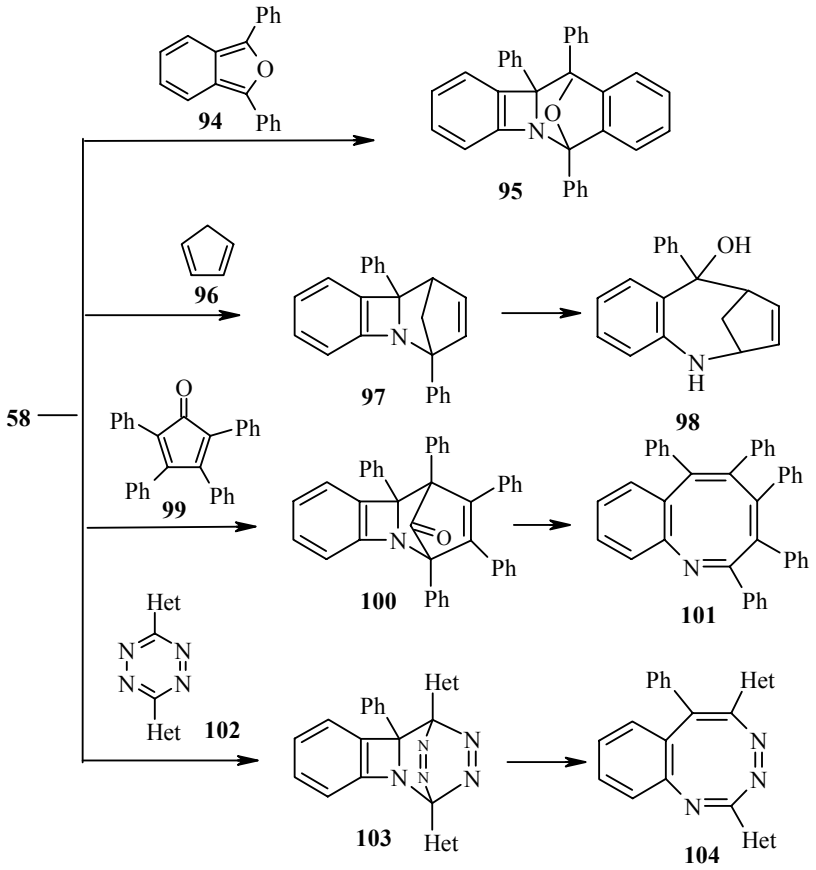
The decomposition of the triazine **57** under the conditions of flash-vacuum pyrolysis was studied, and in this case the yield of the azete **58** amounted to 64% [43]. Photolysis (λ = 300 nm) of the triazine **57** in tetrahydrofuran at room temperature gave the dimer **93a** with a lower yield (43%), but the degree of conversion here was appreciably higher. During photolysis at -80°C the yield of the dimer amounted to only 21% [42]. It was shown that the dimerization of the azete **58** is sensitive to catalysts. Thus, in the presence of Lewis acids ($AlCl_3$, $AgBF_4$, or BF_3–Et_2O) the linear dimer **93b** is also formed with a yield of 20% in addition to the angular dimer **93a** [42].



With conjugated dienes the azete **58** enters into Diels–Alder reactions, leading to cycloaddition products. Examples of such reactions are presented below in a general scheme. Thus, when a solution of diphenylisobenzofuran **94** in dichloromethane is added to the pyrolyzate at -78°C the isoquinoline derivative **95** is formed with a yield of 54% [43]. In other cases the initial adducts are transformed under the reaction conditions into more stable compounds. For example, the tetracyclic product **97** formed from the azete **58** and cyclopentadiene **96** (solvent dichloromethane, -78°C) underwent hydration during chromatographic isolation on silica gel and was converted into the tricyclic alcohol **98** with a yield of 36% [43].

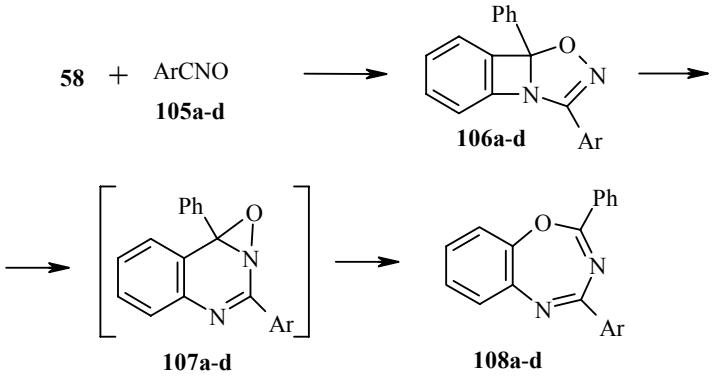
During the treatment of the pyrolyzate containing the azete **58** with a solution of tetraphenylcyclopentadienone **99** in dichloromethane (−78°C), followed by heating the reaction mixture to room temperature, removal of the solvent, and chromatography of the residue on silica gel (eluent 1:9 ether–petroleum ether) 2,3,4,5,6-pentaphenylbenzazocine **101** was obtained with a yield of 52% as a result of the elimination of CO from the initially formed adduct **100** [43].

When another diene, dipyridyl-substituted tetrazine **102**, was used under analogous conditions the initially formed compound **103** was converted into benzotriazocine **104** (yield 25%) with the release of nitrogen [43].



102–104 Het = 2-pyridyl

Examples of the reaction of the benzazete **58** with 1,3-dipoles are also known. Thus, its reactions with the nitrile oxides **105a-d** give the extremely reactive compounds **106a-d**, which readily rearrange to the final products 1,3,5-oxadiazepines **108a-d** through the possible intermediate oxaziridines **107a-d** [52].



105–108 a Ar = Ph, **b** Ar = *p*-C_6H_4Me, **c** Ar = *p*-C_6H_4Cl, **d** Ar = $C_6H_4NO_2$-*p*

We note that the benzazete **58** does not react with dienophiles – cyclopentene, but-2-yne, N-phenyl-maleimides, and 1-diethylaminopropyne [43].

It is seen from the material presented above that benzazetines and their derivatives are highly reactive compounds that enter into various chemical transformations. Their chemical and particularly their biological characteristics have so far been insufficiently investigated. The authors hope that the present review will help to attract the attention of chemists and biologists toward a more intensive and thorough investigation of this interesting class of heterocyclic compounds.

REFERENCES

1. E. M. Burgess and G. Milne, *Tetrahedron Lett.*, 93 (1966).
2. E. M. Burgess and L. McCullagh, *J. Am. Chem. Soc.,* **88**, 1580 (1966).
3. N. H. Cromwell and B. Phillips, *Chem. Rev.,* **79**, 331 (1979).
4. M. D. Mashkovskii, *Drugs* [in Russian], Novaya Volna, Moscow (2000), Vol. 2, p. 221.
5. Y. Deiaegher, N. M. Kuz'menok, A. M. Zvonok, and N. D. Kimpe, *Chem. Rev.,* **102**, 29 (2002).
6. G. S. Singh, *Tetrahedron*, **59**, 7631 (2003).
7. D. Barton and W. D. Ollis (editors), *Comprehensive Organic Chemistry* [Russian translation], Vol. 8, Khimiya, Moscow (1985), p. 704.
8. K. Wojciechowski, *Polish J. Chem.*, **71**, 1375 (1997).
9. K. Wojciechowski, *Eur. J. Org. Chem.*, 3587 (2001).
10. V. I. Potkin, V. A. Zapol'skii, V. A. Knizhnikov, R. V. Kaberdin, A. A. Yanuchok, and S. K. Petkevich, *Zh. Org. Khim.*, **37**, 727 (2001).
11. V. I. Potkin, R. V. Kaberdin, V. A. Zapol'skii, and N. I. Nechai, in: *XVI Mendeleev Conference on General and Applied Chemistry* [in Russian], Vol. 1, Moscow (1998), p. 252.
12. V. I. Potkin, R. V. Kaberdin, V. A. Zapol'skii, N. I. Nechai, and A. A. Yanuchok, in: B. G. Kartsev and G. A. Tolstikov (editors) *Nitrogen Heterocycles and Alkaloids* [in Russian], Vol. 2, Iridium Press, Moscow (2001), p. 239.
13. V. A. Azarko, V. I. Potkin, V. E. Agabekov, R. V. Kaberdin, E. V. Sharendo, and N. I. Nechai, *Vestsi NAN Belarusi. Ser. Khim. Navuk*, No. 4, 44 (2000).
14. G. Ege, *Chem. Ber.*, **101**, 3079 (1968).
15. G. Ege and F. Pasedach, *Chem. Ber.*, **101**, 3089 (1968).
16. G. Ege, E. Beisiegel, and Ph. Arnold, *Chem. Ber.*, **105**, 2898 (1972).
17. R. Dunkin, M. A. Lynch, R. Withnall, A. J. Boulton, and N. Henderson, *J. Chem. Soc, Chem. Commun.*, 1777 (1989).
18. N. Bashir and Th. Gilchrist, *J. Chem. Soc., Perkin Trans. 1,* 868 (1973).
19. M. F. G. Stevens, *J. Chem. Soc., Perkin Trans. 1,* 615 (1974).
20. G. U. Baig and M. F. G. Stevens, *J. Chem. Soc., Perkin Trans. 1,* 999 (1984).
21. G. U. Baig and M. F. G. Stevens, *J. Chem. Soc., Perkin Trans. 1,* 2765 (1984).
22. M. Lancaster and D. J. H. Smith, *J. Chem. Soc., Chem. Commun.,* 471 (1980).
23. A. Chrotowska, F. Gracian, J.-M. Sotiropoulos, G. Pfister-Guillonzo, and K. Wojciechowski, *Eur. J. Org. Chem.,* 313 (2000).
24. M. Letulle, P. Guenot, and J.-L. Ripoll, *Tetrahedron Lett.,* **32**, 2013 (1991).
25. G. Pfister-Guillonzo, F. Gracian, A. Senio, M. Letulle, and J.-L. Ripoll, *Tetrahedron Lett.,* **33**, 5753 (1992).
26. W. Sander and J. Morawietz, *Tetrahedron Lett.,* **34**, 1913 (1993).
27. J. Morawietz, W. Sander, and M. Traubel, *J. Org. Chem.,* **60**, 6368 (1995).
28. R. A. Olofson, R. K. Vander Meer, and S. Stournas, *J. Am. Chem. Soc.*, **93**, 1543 (1971).

29. R. A. Olofson, R. K. Vander Meer, D. H. Hoskin, M. Y. Bernheim, S. Stournas, and D. S. Morrison, *J. Org. Chem.*, **49**, 3367 (1984).
30. V. I. Potkin, V. A. Zapol'skii, R. V. Kaberdin, V. A. Knizhnikov, and A. A. Yanuchok, in: *Book of Abstracts 17th International Congress of Heterocyclic Chemistry,* Vienna, 1999, PO-218.
31. V. I. Potkin, in: *Organic Chemistry in Belarus at the Frontier of the 21st Century, Program and Abstracts* [in Russian], Minsk (1999), p. 18.
32. V. I. Potkin, V. A. Zapol'skii, V. A. Knizhnikov, R. V. Kaberdin, A. A. Yanchuk, and S. K. Petkevich, in: *Organic Chemistry in Belarus at the Frontier of the 21st Century, Program and Abstracts* [in Russian], Minsk (1999), p. 128.
33. V. V. Perekalin, A. S. Sopova, and E. S. Lipina, *Unsaturated Nitro Compounds* [in Russian], Khimiya, Leningrad (1982).
34. K. K. Singal and J. Kaur, *Synth. Commun.*, **31**, 2809 (2001).
35. P. Beak and G. W. Selling, *J. Org. Chem.*, **54**, 5574 (1989).
36. H. Tomioka, N. Ichikawa, and K. Komatsu, *J. Am. Chem. Soc.*, **115**, 8621 (1993).
37. M. Fischer and F. Wagner, *Chem. Ber.,* **102**, 3486 (1969).
38. M. Ikeda, S. Matsugashita, F. Tabusa, H. Ishibashi, and I. Tamura, *J. Chem. Soc., Chem. Comm.,* 575 (1975).
39. E. Ziegler and H. Sterk, *Monatsh. Chem.*, **99**, 1958 (1968).
40. K. Krohn, D. Carboo, and U. Puttfarcken, *Leibigs Ann. Chem.,* 608 (1978).
41. B. M. Adger, M. Keating, Ch. W. Rees, and R. C. Storr, *J. Chem. Soc.*, 19 (1973).
42. Ch. W. Rees, R. C. Storr, and P. J. Whittle, *J. Chem. Soc., Chem. Comm.*, 411 (1976).
43. B. M. Adger, Ch. W. Rees, and R. C. Storr, *J. Chem. Soc., Perkin Trans. I*, 45 (1975).
44. Ch. W. Rees, R. C. Storr, and P. J. Whittle, *Tetrahedron Lett*, 4647 (1976).
45. Ch. W. Rees, *The Chemistry of Benzazetes,* in*:* R. B. Mitra, N. R. Fyyangar, V. N. Gogte, R. M. Acheson, and N. Cromwell (editors) *New Trends in Heterocyclic Chemistry (Studies in Organic Chemistry)*, Elsevier, Amsterdam (1979), Vol. 3, p. 356.
46. M. Fischer, *Chem. Ber.,* **102**, 3495 (1969).
47. V. I. Potkin, V. M. Zelenkovskii, R. V. Kaberdin, and A. A. Yanuchok, *Dokl. NAN Belarusi*, **45**, 72 (2001).
48. V. I. Potkin, V. A. Knizhnikov, A. A. Yanuchok, and R. V. Kaberdin, *Zh. Org. Khim.*, **37**, 680 (2001).
49. V. I. Potkin, S. K. Petkevich, N. I. Nechai, and R. V. Kaberdin, *Zh. Org. Khim.*, **40**, 762 (2004).
50. R. K. Vander Meer and R. A. Olofson, *J. Org. Chem.*, **49**, 3373 (1984).
51. R. A. Olofson and R. K. Vander Meer, *J. Org. Chem.*, **49**, 3377 (1984).
52. Ch. W. Rees, R. Somanathan, R. C. Storr, and A. D. Woolhouse, *J. Chem. Soc., Chem. Comm.,* 740 (1975).