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Acetylenic derivatives of quinones

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Abstract. Methods for the preparation and various transformations of acetylenic derivatives of quinones, which are key intermediates in the synthesis of fused heterocyclic quinoid structures and some highly unsaturated compounds, are surveyed in detail. The bibliography includes 114 references.

I. Introduction

Quinones belong to a unique class of organic compounds, which have a broad spectrum of practical applications.[1–3] Quinone derivatives are traditionally used as dyes, pigments, photomaterials and pharmaceuticals. In recent years, these compounds have found application also as luminophores, laser media, catalysts for chemical processes, *etc*. The latter half of the 20th century has witnessed a rapidly growing interest in biologically active quinones and quinoid compounds. This interest is associated with the fact that both natural quinones (anthracycline, mitomycin and anthrapyran antibiotics) and a series of structurally simple synthetic derivatives were found to exhibit antitumour activity. Some of these compounds were integrated into medical practice. Later on, it was revealed that quinoid compounds possess other physiological activities, including antibacterial, antiviral and fungicidal activities, and exhibit radiosensitising properties. New classes of antibiotics and biologically active pigments were found. An extensive search for new pharmacophore structures, elucidation of the structure – biological activity relationship for quinoid compounds and the synthesis of complex natural products and their analogues called for an extension and upgrade of the traditional synthetic base for investigation of this class of compounds. The problems to be solved included not only the development and application of new synthetic approaches but also the possible uses of new starting compounds, key intermediates and new reagents.

Systematic studies of acetylenic derivatives of the simplest quinones (benzo-, naphtho- and anthraquinones) were started in the late 1970s and the early 1980s.[4–10] Due to the simultaneous presence of two highly reactive fragments, *viz*., the quinoid moiety and the acetylenic group, influencing each other, these compounds were considered as intermediates in the synthesis of more complex quinoid structures. It was also expected that some acetylenic derivatives could be used as precursors of highly reactive unsaturated compounds of other classes. Besides, the possibility that these compounds, particularly, functionally substituted derivatives, could exhibit targeted biological action was not ruled out.

Extensive experimental data on the chemistry of alkynylquinones are presently available. Procedures were developed for the synthesis of these compounds, their chemical characteristic features were revealed and new chemical reactions were discovered and studied. However, the available data on the chemistry of alkynylquinones were not generalised. The aim of the present review is to close this gap, survey, as exhaustively as possible, the results of these investigations published in the literature and to call the attention of chemists to this promising group of polyfunctional compounds for the purpose of extending the scope of application of these derivatives in fine organic synthesis.

II. Synthesis methods

1. Cross-coupling of haloquinones with terminal acetylenes

Presently, cross-coupling of haloquinones with terminal acetylenes is recognised as the most versatile method for the synthesis of acetylenic derivatives of quinones. This method is based on the replacement of halogen atoms in carbo- and heteroaromatic rings as well as in vinyl halides by acetylenic groups.[11,12] Two main versions of this reaction, the catalytic and so-called acetylide, are generally used. In the catalytic version, aryl halides are condensed with terminal acetylenes in the presence of Pd(II) or Pd(0) triphenylphosphine complexes, cuprous iodide and a base (generally, amine). In the acetylide version, either condensation is performed directly with Cu(I) acetylide or the latter is prepared *in situ* from terminal acetylene in the presence of CuI and potassium carbonate. In both versions, the reactions are carried out under an inert atmosphere to prevent oxidative dimerisation of terminal acetylenes. In all cases, the reactivity of aryl halides decreases in the series ArI > ArBr > ArCl.

a. Catalytic method

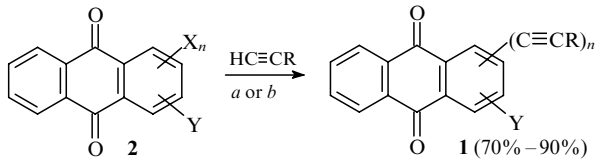
Efficient cross-coupling in the presence of a combined Pd – Cu catalyst is used to introduce acetylenic substituents into the benzene rings of halogen derivatives of 9,10-anthra- and 1,4-naphthoquinones. The reactions are usually performed in an excess of amine (Et_3N or Et_2NH), which serves as a solvent and base, in the presence of $Pd(PPh_3)_2Cl_2$ and CuI at high temperature.[13–15] In some cases, amine is used in combination with an inert solvent[16] or, alternatively, an inorganic base (for example,

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K_2CO_3) in pyridine, DMF or dioxane is employed.[10, 17, 18] Iodine-containing quinones are reagents of choice. However, cheaper bromides were also successfully used in the synthesis of long-chain acetylenic derivatives of functionalised anthraquinones (components of coloured liquid-crystalline composites).[16] The chlorine atoms in the benzene rings of quinones are inactive.[10, 15]

In such catalytic systems, a series of acetylenic derivatives **1** were synthesised from mono- and polyiodo(bromo)anthraquinones **2**. The products were usually prepared in 70% – 90% yields, and the reaction time was 0.5 – 3 h.



X = I, Br; n = 1, 2; Y = H, NH_2, NHMe, Cl, OCOPh;

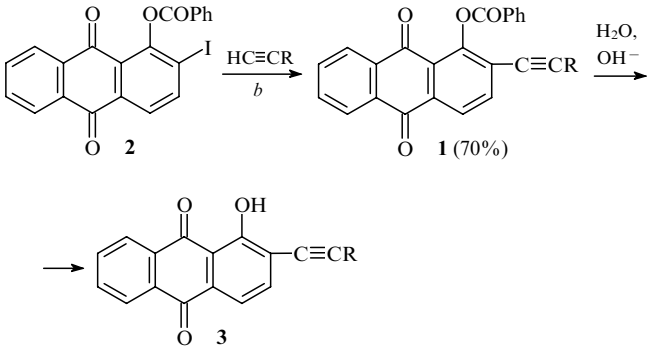
R = C_5H_{11}, C_7H_{15}, CMe_2OH, CH_2N O, Ph;

(*a*) $Pd(PPh_3)_2Cl_2$ – CuI, Et_3N or Bu_3N; 50 – 90 °C;

(*b*) $Pd(PPh_3)_2Cl_2$ – CuI, K_2CO_3; Py, DMF or dioxane; 50 – 90 °C.

In both systems (*a* and *b*), the reactivity of 2-iodo-substituted isomers is comparable with that of 1-iodoanthraquinones.[10, 14] However, the presence of a bulky substituent at position 2 of the latter slows down the reaction due, apparently, to steric factors,[19] which hinder the formation of organopalladium complexes. For example, the reactions of methyl 1-iodoanthraquinone-2-carboxylate with terminal acetylenes, unlike those of 1-iodoanthraquinone, proceed slowly and ambiguously and are accompanied by substantial resinification.

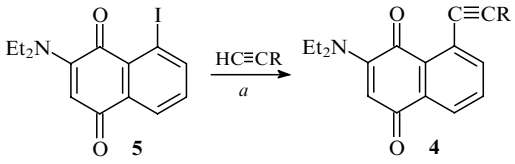
These cross-coupling reactions of haloanthraquinones with acetylenes have virtually no limitations on the nature and arrangement of functional substituents in the starting compound. However, if the quinone moiety of the starting compound contains the hydroxy group adjacent to the halogen atom, the reaction results in intramolecular cyclisation of the primary condensation product, *viz*., hydroxyacetylene (see Section III.3.a). A standard procedure for the protection of the hydroxy group was used in the study.[17] Benzoyloxy derivative **2** (X = 2-I, Y = 1-OCOPh) in the presence of a weak nucleophilic base (K_2CO_3) in pyridine produced alkynyl(benzoyloxy)quinones,[17] whose subsequent alkaline hydrolysis afforded compounds **3**.



R = CMe_2OH, Ph;

(*b*) $Pd(PPh_3)_2Cl_2$ – CuI, K_2CO_3, Py; 50 – 90 °C.

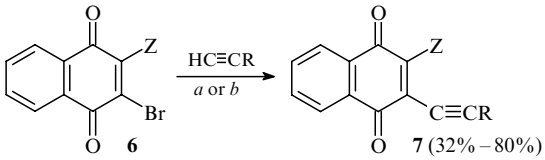
Cross-coupling of halogen derivatives of 1,4-naphthoquinone with acetylenes is complicated by high electrophilicity of the quinoid ring. This ring can be blocked by introducing a strong electron-donating substituent. The efficiency of this protection was exemplified by the synthesis of compounds **4** from 3-diethylamino-5-iodo-1,4-naphthoquinone **5**.[13]



R = CMe_2OH, Ph;

(*a*) $Pd(PPh_3)_2Cl_2$ – CuI, Et_3N or Et_2NH; 50 – 90 °C.

Catalytic cross-coupling is used also for the introduction of acetylenic substituents into the quinoid ring of 1,4-naphthoquinone derivatives **6** to prepare compounds **7**.[20] In these reactions, the molecule is stabilised by the functional group, which is present in the quinoid ring and possesses a strong positive mesomeric effect.



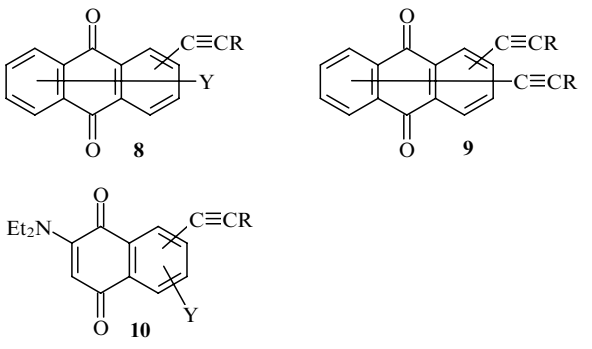
Z = NMe_2, N , N , OEt;

R = C_8H_{17}, CH_2OH, CH_2OMe, CH_2OAc, CH_2OPh, CMe_2OH, CMe_2OMe, CH_2N O, Ph;

(*a*) $Pd(PPh_3)_2Cl_2$ – CuI, Et_3N or Et_2NH; 50 – 90 °C;

(*b*) $Pd(PPh_3)_2Cl_2$ – CuI, K_2CO_3; Py or DMF; 50 – 90 °C.

Cross-coupling of acetylenes with quinones containing halogen atoms in the benzene rings is substantially intensified in an aqueous – organic medium (water – dioxane or water – pyridine mixtures) in the presence of the same Pd and Cu catalysts and an inorganic base (Na_2CO_3, K_2CO_3, $NaHCO_3$ or AcONa).[14 – 18, 21 – 31] The reaction time is an order of magnitude shorter than that in anhydrous media and is, as a rule, 5 – 30 min at 70 – 90 °C. This procedure was used in the synthesis of numerous acetylenic derivatives of quinones **8** – **10** (yields were 48% – 98%). It allows one to perform cross-coupling of haloquinones with labile acetylenes, for example, with ethyl propiolate.[25, 26] It should be noted that attempts to carry out condensation of the latter with aryl iodides in anhydrous media under standard conditions failed.[32]



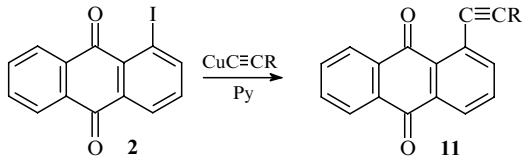
R = , CH_2OH, CH(OH)Pr, CMe_2OH, , , CH(OH)Ph, CH_2OPh, CO_2Et, CH_2N , Ph;

Y = NH_2, NHMe, NO_2, Cl.

Due to a high rate of the reaction in an aqueous – organic system, labile alkynylquinones can be prepared in rather high yields.

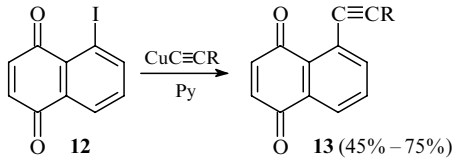
b. Acetylide method

Cross-coupling of quinones with cuprous acetylides in the absence of palladium complexes is used for the introduction of acetylenic substituents exclusively into the benzene rings of quinones. Due to the influence of electron-withdrawing groups conjugated with the benzene ring, the halogen atoms in the latter possess rather high nucleofugicity and can be replaced by acetylenic groups under relatively mild conditions (moderate temperature, moderate nucleophilicity of the medium and the absence of a strong base). For comparison, 1-iodonaphthalene reacts with Cu(I) phenylacetylide in pyridine at 115 °C for 10 h.[33] By contrast, the reaction of 1-iodoanthraquinone **2** (X = 1-I, Y = H) with phenylacetylide is completed in 1.5 h at 90 °C [10] and the reaction with butylacetylide is completed in 40 min at 60 °C to give the corresponding alkynylanthraquinones **11**.[23]

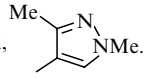


R = Bu, Ph.

Under these conditions, halonaphthoquinones with unsubstituted quinoid rings can also be introduced into reactions with cuprous acetylides. For example, 5-iodo-1,4-naphthoquinone **12** reacts with Cu(I) aryl- and hetarylacetylides in pyridine at 50 – 80 °C for 5 – 25 min to form the corresponding products **13**.[34]

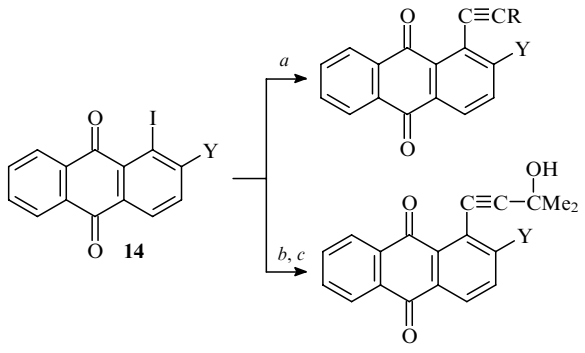


R = Ph, *p*-$MeOC_6H_4$, *p*-$Me_2NC_6H_4$, *p*-$O_2NC_6H_4$,

2-naphthyl, 

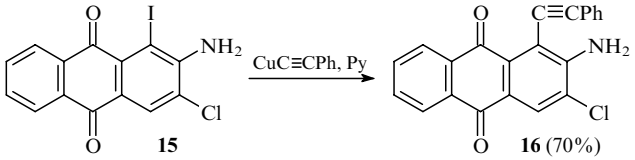
The iodine atom at the β position of the benzene ring of quinone is less easily replaced under the action of Cu(I) acetylides compared to that at the α position.[10] The reaction of 2-iodoanthraquinone with Cu(I) phenylacetylide proceeds ~20 times more slowly than that of 1-iodoanthraquinone.

Functionalised iodoquinones are, as a rule, readily condensed with acetylides, electron-withdrawing substituents noticeably accelerating the reaction.[10, 17 – 19, 23, 24, 35 – 37] 1-Iodoanthraquinones **14** bearing bulky substituents at position 2, which hinder Pd-catalysed condensation, react without complications with both Cu(I) acetylides and terminal acetylenes in the presence of Cu(I) salts and K_2CO_3.[19, 23, 30, 35, 37] The catalytic method can be applied to terminal acetylenes, which do not form acetylides stable in the solid state.



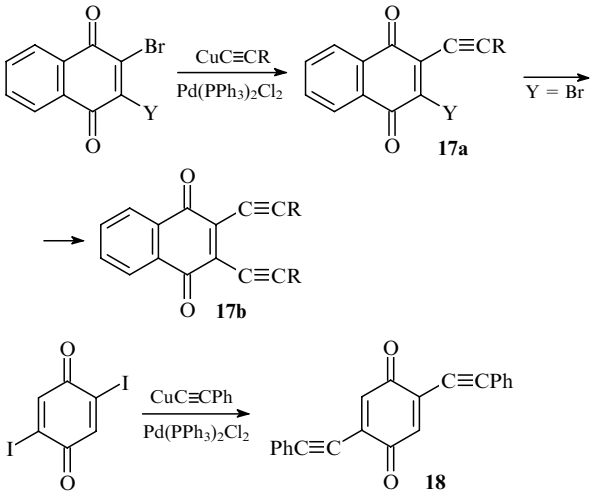
Y = CO_2Me, $CH(OEt)_2$, CHO; R = Bu, CH_2OPh, Ph;
(*a*) CuC≡CR, Py; (*b*) HC≡$CCMe_2OCH(OEt)Me$, K_2CO_3, CuI, Py;
(*c*) H_3O^+.

Under various conditions, copper-mediated condensation of vicinal hydroxy(halo)quinones results in intramolecular cyclisation to form the furan ring (see Section III.3.a).[38, 39] Unlike this reaction, condensation of *vic*-amino(iodo)anthraquinones with Cu(I) acetylide can be terminated in the step of formation of an acetylenic derivative of aminoanthraquinone. Under more drastic conditions, the latter undergoes cyclisation in the presence of an excess of acetylide to give the corresponding naphthoindoledione (see Section III.2.a).[18] For example, the reaction of 2-amino-3-chloro-1-iodoanthraquinone (**15**) with Cu(I) phenylacetylide in pyridine at 20 °C for 30 min affords 2-amino-3-chloro-1-phenylethynylanthraquinone (**16**).



The *vic*-amino group facilitates the replacement of the halogen atom under the action of Cu(I) acetylides. For instance, the reaction of 1-amino-2-iodoanthraquinone with Cu(I) phenylacetylide in pyridine at 80 °C is completed in 2.5 h [18] (for 2-iodoanthraquinone, the reaction time is 26 h at 90 °C).[10]

The reactions of quinones containing halogen atoms in the quinoid ring with Cu(I) acetylides under rather mild conditions proceed only in the presence of the Pd catalyst.[40] The reactions are carried out in a mixture of DMSO and $CHCl_3$ at 20 – 50 °C. Condensation can be performed with both Cu(I) acetylides as such and acetylides prepared *in situ* from terminal acetylene, CuI and Et_3N. The second approach is used only if it is impossible to isolate stable acetylides in the solid state. The yields of alkynylquinones **17** and **18** vary from 35% to 84%.



R = CMe_2OH, CMe_2OMe, 

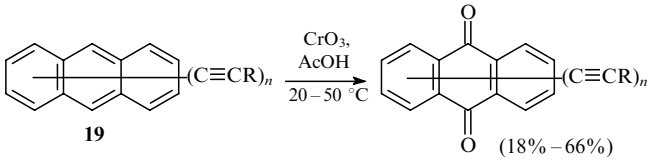
, Ph, *p*-$MeOC_6H_4$, *p*-$O_2NC_6H_4$;

Y = H, Br, NHAc, N(Ac)Ph, OEt.

2. Oxidation of alkynylarenes

Oxidation of aromatic compounds is one of the most general methods for the synthesis of quinones.[1 – 3, 41] Owing to the stability of the triple bond with respect to certain reagents, which can oxidise arenes to quinones, alkynylarenes can be used for the preparation of alkynylquinones.

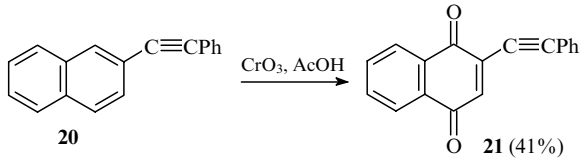
Anthracenes **19** containing acetylenic substituents in the flank rings are readily oxidised with CrO_3 in 80% AcOH with retention of the triple bonds.[5, 7, 29] This procedure allows one to prepare 9,10-anthraquinones with various sets of acetylenic substituents.



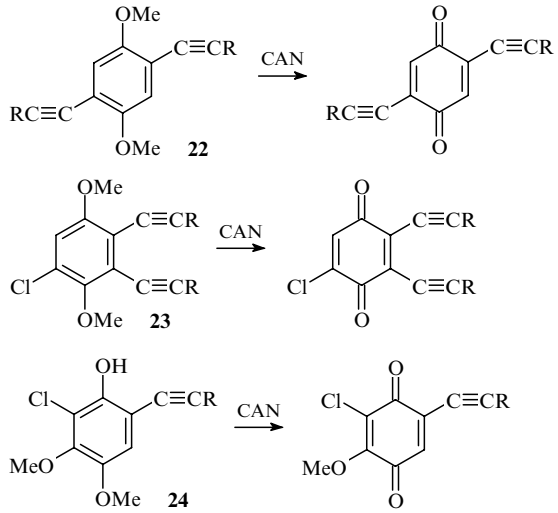
R = H, CH_2N O, COPh, *p*-$MeOC_6H_4$, *p*-$O_2NC_6H_4$, Ph; $n = 1, 2$.

The time of oxidation depends on the concentration of the substrate and the reaction temperature and varies over a wide range (5 – 240 min). Under these conditions, oxidation of 1,8-dialkynylanthracenes is sensitive to the nature of a substituent at the triple bond. For example, an attempt to oxidise 1,8-diethynylanthracene failed, whereas 1,8-bis(phenylethynyl)anthracene was oxidised at 60 °C for 6 min to form the corresponding anthraquinone in 31.5% yield.[7]

2-Phenylethynylnaphthalene (**20**), which contains no other substituents in the aromatic nucleus, is oxidised also with CrO_3 in 80% AcOH, the substituted ring being subjected to oxidation to give 2-phenylethynyl-1,4-naphthoquinone (**21**).[5]

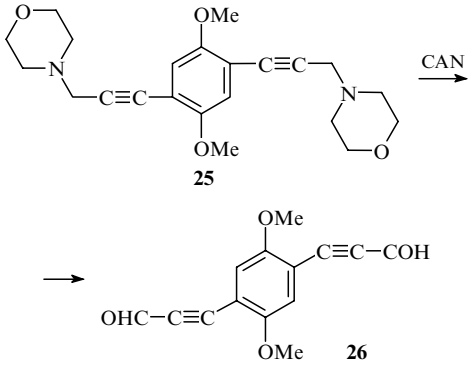


Aromatic compounds bearing two OR groups (R = H and/or Me) at the *para* positions are readily oxidised with Ce(IV) salts to give quinones.[1] These oxidising agents leave the triple bond intact and are used in the synthesis of various (mono- and polycyclic) quinones with acetylenic substituents in the benzene or quinoid ring.[5,8] For example, acetylenic derivatives of 1,4-dimethoxy- and 1-hydroxy-4-methoxybenzenes **22** – **24** were oxidised to the corresponding 1,4-benzoquinones with ammonium cerium nitrate (CAN) in aqueous MeCN or THF at room temperature.[5,8,42]



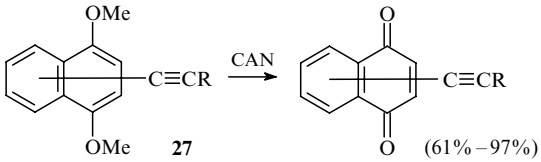
R = Bu, CMe_2OH, CH_2OCH_2Ph, Ph, *p*-$MeOC_6H_4$.

This reaction has a number of limitations. Oxidation proceeds satisfactorily in the presence of electron-donating or weak electron-withdrawing groups at the triple bond (yields are 40% – 89%). Strong electron-withdrawing groups, such as *p*-$O_2NC_6H_4$ or PhCO, hinder the reaction.[8] The substrate also remains non-oxidised if it forms an insoluble complex salt with the oxidising reagent [an example is 2,5-bis(2-pyridylethynyl)-1,4-dimethoxybenzene]. If the side chain of the substrate contains functional groups readily oxidised with cerium(IV), the reaction can afford other oxidation products. For instance, oxidation of 2,5-bis(3-morpholinoprop-1-ynyl)-1,4-dimethoxybenzene (**25**) with CAN gave rise to unsaturated dialdehyde **26** (in 46.5% yield) rather than quinone.



Unsuccessful attempts to prepare some alkynylquinones may also be associated with their lability. For example, an attempt to synthesise 2,5-diethynyl-1,4-benzoquinone from 2,5-diethynyl-1,4-dimethoxybenzene ended in failure.[8]

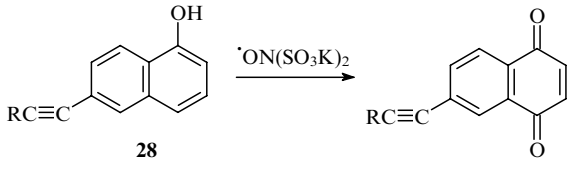
Depending on the structure of the starting compound, oxidation of acetylenic derivatives of 1,4-dimethoxynaphthalene **27** with ammonium cerium nitrate affords 1,4-naphthoquinones containing the substituent with the triple bond in either the quinoid or benzene ring. This procedure was used for the synthesis of 2-, 5- and 6-alkynyl-1,4-naphthoquinones.[5,8,13,43]



R = H, Ph.

In some cases, hydroquinones and their ethers are oxidised to quinones with Ag salts. For example, 2-hydroxymethyl-3-(3-methylbut-3-en-1-ynyl)hydroquinone, which is a metabolite of the natural antibiotic frustulosin, was oxidised with silver carbonate on celite in benzene.[44]

Potassium nitrosodisulfonate (fremy's salt) is a specific oxidising reagent, which allows one to transform aromatic amines and phenols into quinones under mild conditions.[45] This salt was used for oxidation of 1-naphthols **28** containing acetylenic substituents at position 6.[43] The reaction was carried out at 20 °C in an aqueous – methanolic solution of KH_2PO_4.



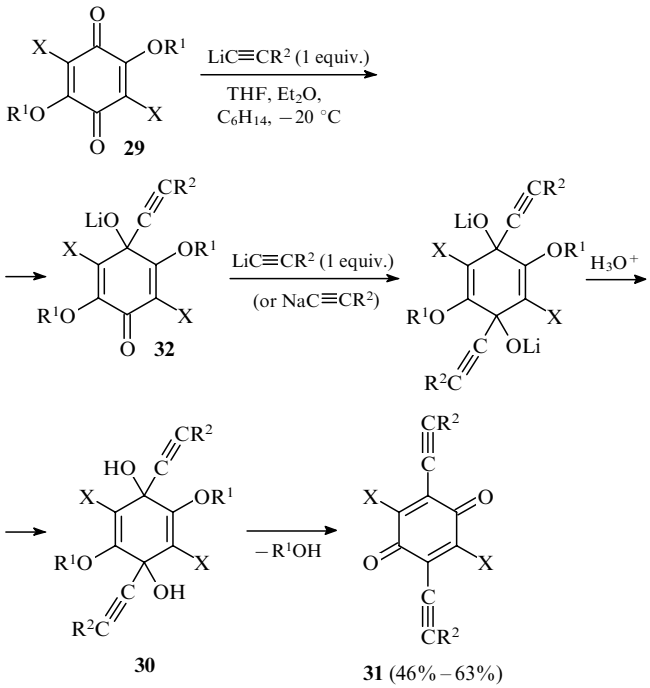
R = H, CMe_2OH, Ph.

On the whole, oxidation of aromatic acetylenic derivatives as a method for the synthesis of alkynylquinones has not been adequately investigated. However, there is no doubt that the scope of this method can be substantially extended.

3. Synthesis of acetylenic derivatives of *para*- and *ortho*-benzoquinones from dialkoxybenzoquinones

Moore and co-workers[4,6,9,42] developed an original procedure for the preparation of alkynylbenzoquinones from dialkoxy derivatives **29**. The synthesis involves the addition of lithium acetylides at the carbonyl groups of the starting quinone followed by acid hydrolysis of vinyl ether fragments of the resulting glycol **30** accompanied by dehydration. In some cases, the second step is

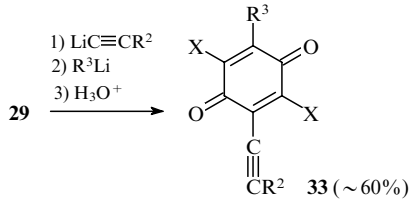
carried out with the use of $(CF_3CO)_2O$ in the presence of concentrated H_2SO_4. As a result of these transformations, the quinoid structure of the ring, which is initially destroyed due to the introduction of acetylenic substituents, is restored. This approach can be exemplified by the synthesis of 2,5-dialkynyl-1,4-benzoquinones **31** from 2,5-dialkoxy-1,4-benzoquinones **29**.[4,6]



X = H, Cl; R^1 = Me, Et; R^2 = CH_2OMe, CH_2OBn, CH_2OTHP (THP is tetrahydropyranyl), CH_2Bn, Ph, *o*-MeC_6H_4, $MeC{=}CH_2$, $SiMe_3$.

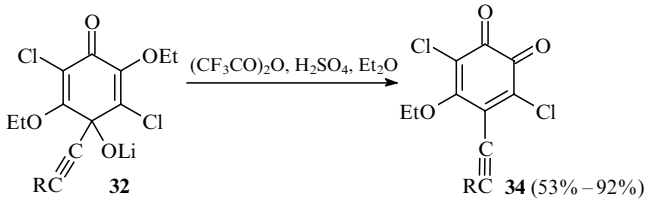
Alkynylation of compounds **29** with some lithium acetylides bearing rather bulky substituents stops at monoadduct **32** or proceeds further very slowly.[42,46] In the latter case, the second step of alkynylation is carried out with the use of sodium acetylides instead of lithium acetylides because the former are less self-associated and, hence, more reactive.[42]

The reaction can be terminated in the step of formation of monoadduct **32** and the latter can be transformed into an unsymmetrical diadduct upon the addition of one equivalent of alkyl- or aryllithium. Hydrolysis and dehydration of the latter afford monoacetylenic *p*-benzoquinones **33**.



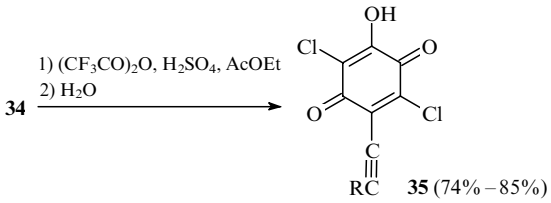
R^2 = CH_2OBn, CH_2OTHP, $(CH_2)_3OTHP$, Ph; R^3 = Me, Ph.

Monoadducts **32** can also serve as precursors of acetylenic derivatives of *ortho*-benzoquinone **34**.[42] In these reactions, a $(CF_3CO)_2O - H_2SO_4$ mixture is used in the second step.



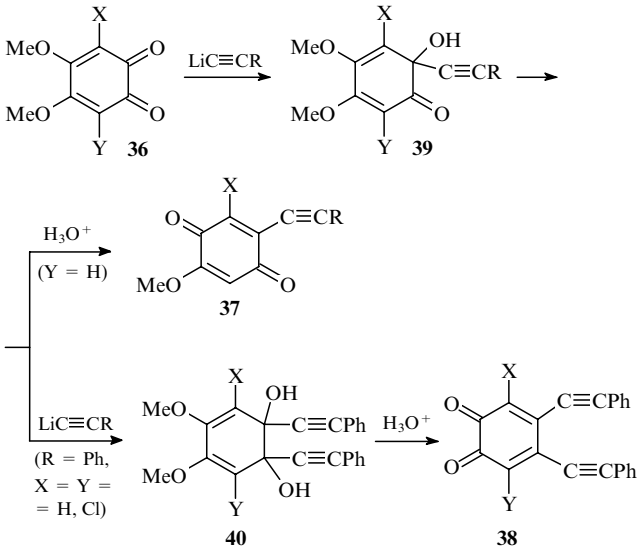
R = H, Bu, CH_2OTHP, $(CH_2)_4C{\equiv}CH$, $(CH_2)_2Ph$, $MeC{=}CH_2$, $CH{=}CHPh$, CO_2Et, Ph, *o*-$MeOC_6H_4$, α-$C_{10}H_7$, $SiMe_3$.

Under more drastic conditions, some 4-alkoxy-5-alkynyl-1,2-benzoquinones **34** can be hydrolysed to 5-alkynyl-2-hydroxy-1,4-benzoquinones **35**.[42]



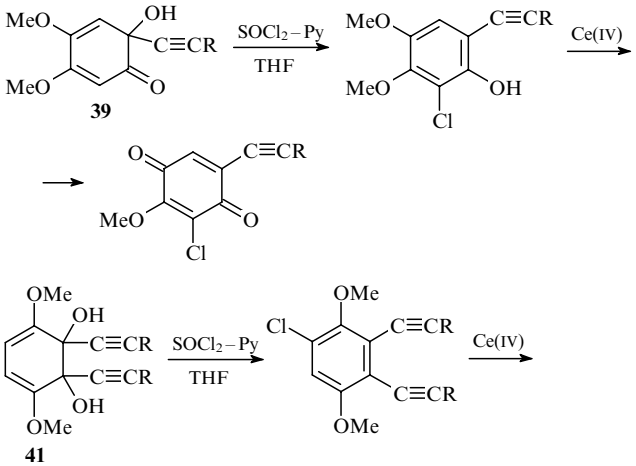
R = H, Bu, $(CH_2)_4C{\equiv}CH$, $MeC{=}CH_2$, CO_2Et.

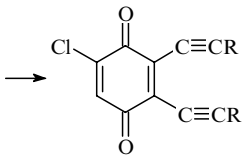
The method developed by Moore and co-workers allows one to prepare 2-alkoxy-5-alkynyl-1,4-benzoquinones **37** and 4,5-dialkynyl-1,2-benzoquinones **38** (in 41% – 90% yields) from 4,5-dialkoxy-1,2-benzoquinones **36** through mono- (**39**) and diadducts **40**, respectively.[9,42]



X = H, Cl, Br; Y = H, Cl; R = H, Pr, Bu, CH_2NEt_2, CH_2OCH_2Ph, $MeC{=}CH_2$, $(CH_2)_4C{\equiv}CH$, CO_2Et, Ph, OEt.

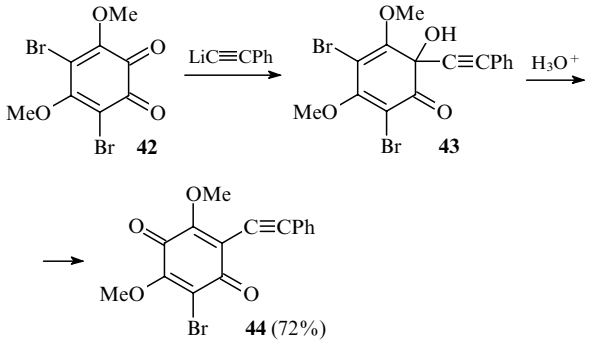
Interestingly, monoadducts **39** (X = Y = H) and diadduct **41** are readily transformed into the corresponding acetylenic derivatives of alkoxy-substituted chlorobenzenes under the action of $SOCl_2$ in THF in the presence of pyridine.[42] These reaction products, in turn, can serve as precursors of mono- or dialkynyl-1,4-benzoquinones (see Section II.2).





R = Bu, CH_2OBn, Ph.

In the reaction of 4,6-dibromo-3,5-dimethoxy-1,2-benzoquinone **42** with lithium phenylacetylide, the latter attacks the carbonyl group at position 2[42] to give monoadduct **43**, which is unstable and readily hydrolysed on treatment. This reaction leaves the methoxy groups intact and gives rise to 2-bromo-3,5-dimethoxy-6-phenylethynyl-1,4-benzoquinone **44**.



Apparently, it is impossible to extend the above-considered procedure for the synthesis of acetylenic derivatives of *p*- and *o*-benzoquinones to naphthoquinone derivatives. Hanhela and Paul[47] attempted to synthesise 1,4-dihydro-2,3-dimethoxy-1,4-di(phenylethynyl)naphthalene-1,4-diol by adding two moles of lithium phenylacetylide to 2,3-dimethoxy-1,4-naphthoquinone followed by reductive aromatisation of the diadduct; however, the reaction afforded a mixture of other products.

4. Other methods

Before the above-described general methods for the synthesis of acetylenic derivatives of quinones were developed, compounds of this class had been prepared according to procedures applicable only to particular cases. For example, bis(anthraquinon-2-yl)acetylene was prepared by reductive cross-coupling of 2-tribromomethylanthraquinone either under the action of copper metal in refluxing nitrobenzene[48] or by thermal condensation of 2-dibromomethylanthraquinone followed by dehalogenation of the resulting substituted dibromoethylene in refluxing diethylaniline or phenol in the presence of K_2CO_3.[49] The addition of chlorine to 1-(anthraquinon-2-yl)-2-(2,4-dinitrophenyl)ethylene followed by dehydrohalogenation of the adduct was used for the synthesis of 2-(2,4-dinitrophenylethynyl)anthraquinone.[50] Dehydrochlorination of a series of functionalised (2-chloro-2-propen-1-yl)anthraquinones was studied.[51,52] Depending on the structure of the starting compound, the chloropropenyl substituent can be transformed into the prop-1-ynyl, propanedienyl or 2-oxopropyl group. If there are two chloropropenyl substituents in the substrate, at least one of them is transformed into the propynyl group. A series of 2-(arylethynyl)anthraquinones were synthesised by the Wittig reaction.[53] Acid-catalysed dehydration of 3-alkynyl-1,2,3,4-tetrahydro-1,3,5,8-tetrahydroxyanthraquinones, in which the acetylenic group is not directly bound to either the quinoid or aromatic ring, afforded 6-alkynyl-1,4-dihydroxyanthraquinones.[54,55]

III. Chemical properties

1. Reactions with amines

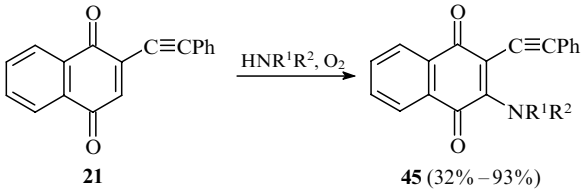
In acetylenic derivatives of quinones, the triple bond is highly electrophilic due to conjugation with carbonyl groups located in the plane of the cyclic moiety of the molecule. These compounds, like other compounds bearing the activated triple bond, can add *N*-nucleophiles, for example, amines.

a. Quinones containing acetylenic substituents in the quinoid ring

Quinones containing acetylenic substituents in the quinoid ring are vinylogs of acetylenic ketones.

The reactions of 2-alkynyl-1,4-naphthoquinones with amines can follow two competitive pathways: addition at the triple bond and oxidative replacement of the hydrogen atom at position 3. The latter reaction involves the Michael-type 1,4-addition of amine to the ketovinyl group of quinone to form 1,4-dihydroxynaphthalene followed by oxidation of the latter.[1]

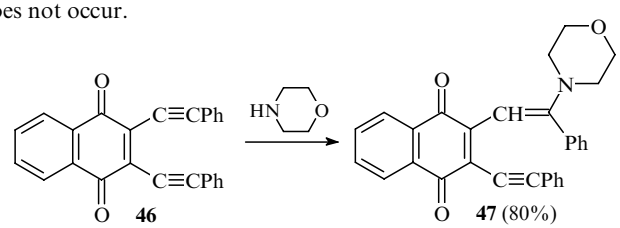
However, of the above two possible pathways, only oxidative amination takes place.[56] For example, 2-phenylethynyl-1,4-naphthoquinone **21** reacts with primary and secondary amines as well as with NH_3 at room temperature to give 2-amino-3-phenylethynyl-1,4-naphthoquinones **45**. Generally, dioxane, aqueous dioxane, diethyl ether or an excess of amine is used as the solvent. An additive of $Cu(OAc)_2$ catalyses oxidation of the hydroquinone intermediate.



$R^1 = R^2 =$ H, Me, Et; $R^1 =$ H: $R^2 =$ Me, Et, cyclo-C_6H_{11}, $(CH_2)_2OH$, CH_2Ph, CH_2CO_2Me, $CH_2CO_2^-$, Ph; $R^1-R^2 = -(CH_2)_5-$, $-(CH_2)_2O(CH_2)_2-$.

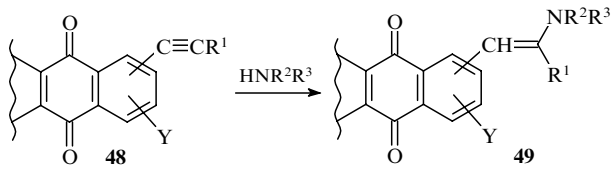
In the reaction with 2-alkynyl-1,4-naphthoquinone containing an electron-withdrawing substituent at position 3 of the quinoid ring, amine adds at the triple bond. The introduction of an electron-donating group (for example, of the amino group) leads to deactivation of the adjacent triple bond. However, acylation of the latter restores the ability of the acetylenic substituent to add amines.[56]

Unlike monosubstituted 2-phenylethynyl-1,4-naphthoquinone, 2,3-bis(phenylethynyl)-1,4-naphthoquinone (**46**) readily adds one equivalent of morpholine (20 °C, 15 min)[56] to give monoadduct **47**. Due to low electrophilicity of the triple bond in the latter compound, the addition of the second amine molecule does not occur.



b. Quinones with an acetylenic substituent in the benzene ring

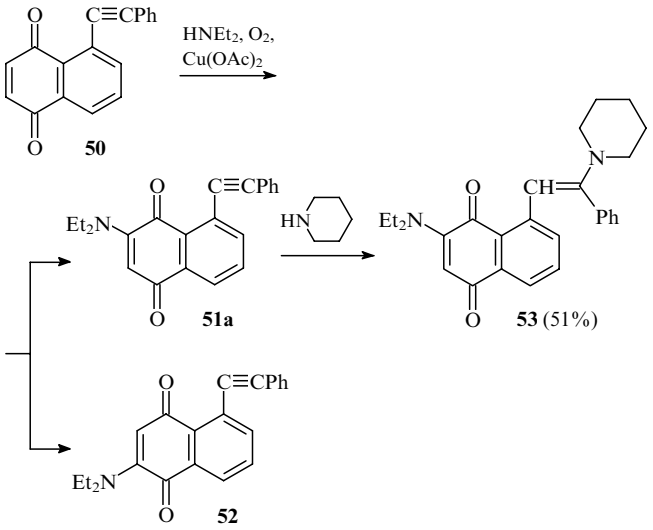
Anthraquinones and naphthoquinones **48** containing an acetylenic substituent in the benzene ring add secondary amines at the triple bond at 20–105 °C in dioxane or in an excess of amine to form adducts **49** in 50%–95% yields.[13,15,19,22,29,57]



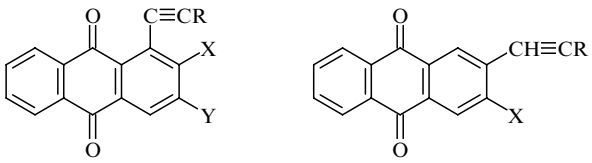
Y = H, Cl, NH_2, NO_2, CO_2Me; R^1 = H, CMe_2OH, CH_2N⟨O⟩, Ph, CH_2OPh; $R^2 = R^3$ = Et, Bu; R^2-R^3 = $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_2O(CH_2)_2-$.

Studies by ^1H NMR spectroscopy demonstrated that these reactions always afford only one geometric isomer. For ethynylquinones (R^1 = H), this isomer has a *trans* configuration.

Naphthoquinones devoid of substituents in the quinoid ring are subjected to oxidative amination at one of its positions. For example, the reaction of 5-phenylethynyl-1,4-naphthoquinone **50** with an excess of amine in the presence of $Cu(OAc)_2$ as the catalyst by bubbling air at 20 °C afforded a mixture of 3- (**51a**) and 2-amino derivatives (**52**) in a ratio of ~2 : 1 in 54.5% yield.[13] In isomer **51a**, the triple bond retains the ability to add amines. However, isomer **51a** forms adduct **53** with piperidine under more drastic conditions (at 80 °C for 10 h).



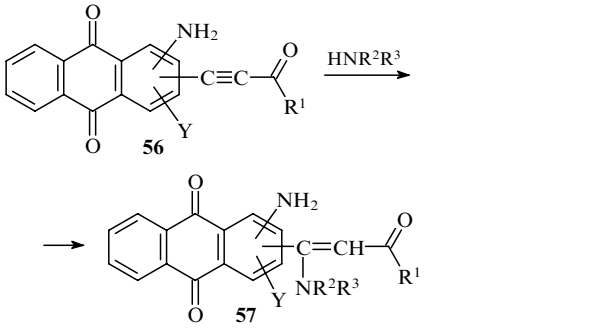
The reactivity of quinones containing an acetylenic substituent in the benzene ring depends on the nature of this substituent, its position and the presence of other functional groups. The acetylenic substituent at the α position of the benzene ring is more active than the substituent at the β position. In both cases, ethynyl derivatives are most reactive. For instance, the reactions of 1-ethynyl- (**54a**) and 2-ethynylanthraquinones (**55a**) with pyrrolidine at 20 °C were completed in 15 min and 12 h, respectively.[15] The reactions of 3-diethylamino-5-ethynyl- (**51b**) and 3-diethylamino-5-phenylethynyl-1,4-naphthoquinone **51a** with piperidine were completed in 1 h at 20 °C and in 10 h at 80 °C, respectively,[13] whereas the reaction time of the addition of piperidine to 2-phenylethynylanthraquinone **55b** at 80 °C was as long as 48 h.[15] The acetylenic substituent and the halogen atom present in the same ring activate each other. In going from 1-phenylethynylanthraquinone (**54b**) to its 2- and 3-chloro-substituted derivatives (compounds **54c**,**d**), the time of the reaction with piperidine decreases from 4 h to 8 and 20 min, respectively (80 °C).[15] The time of the competitive reaction, *viz*., the replacement of the halogen atom in 1-chloroanthraquinone **2** (X = 1-Cl, Y = H) by the piperidine group, decreases in the presence of the phenylethynyl substituent at positions 2 and 4 from 1.5 h to 12 and 20 min, respectively (80 °C). In 3-chloro-2-phenylethynylanthraquinone (**55c**), the addition of piperidine and the replacement of the chlorine atom with piperidine proceed at similar rates. The replacement and addition products (4 : 3 ratio; 79% total yield) do not react with the amine.



54	R	X	Y
a	H	H	H
b	Ph	H	H
c	Ph	Cl	H
d	Ph	H	Cl

55	R	X
a	H	H
b	Ph	H
c	Ph	Cl

In acylethynylanthraquinones, the triple bond is activated both by the carbonyl group of the substituent and the quinone ring. In *vic*-amino(acylethynyl)anthraquinones **56**, the influence of the carbonyl group prevails and the addition of amine occurs at the β position with respect to the carbonyl group[36, 39, 58] to give adducts **57** in 69% – 75% yields.



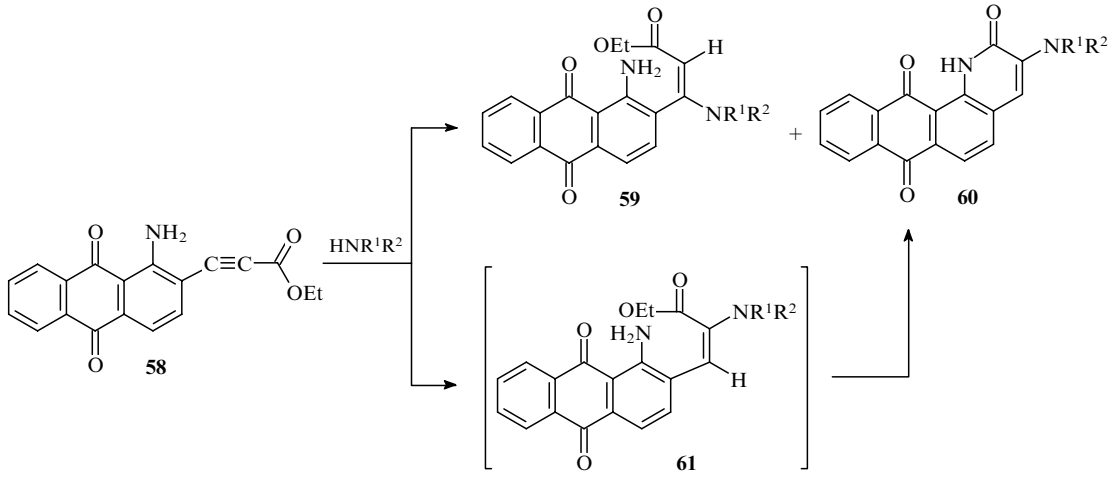
Y = H, Cl, NO_2; R^1 = Ph, Bu^t; R^2 = H: R^3 = Bu, C_8H_{17}; $R^2 = R^3$ = Et; R^2-R^3 = $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_2O(CH_2)_2-$.

Unlike ketones **56**, ethyl (1-aminoanthraquinon-2-yl)propiolate (**58**) adds amines to form two products, *viz*., the corresponding β-amino acrylate **59** (in 60% – 66% yields) and 1*H*-3-aminonaphtho[2,3-*h*]quinoline-2,7,12-trione **60** (in 12% – 18% yields).[25, 26] Evidently, the latter products are generated through rapid cyclisation under the conditions of the reaction of regioisomeric α-amino acrylates **61** (Scheme 1).

Apparently, the ease of intramolecular cyclisation of α-amino acrylates of type **61** as well as of the resulting β-amino acrylates (see Section III.4) indicates that the adducts of both types have an *E* configuration. Taking into account the regioselectivity of the addition of amines to acylethynylanthraquinones and the ratio between the yields of linear and cyclic products of addition to aminoanthraquinonyl propiolate **58**, the groups activating the triple bond can be arranged in the following series: CO > CO_2Et > 1-aminoanthraquinon-2-yl.

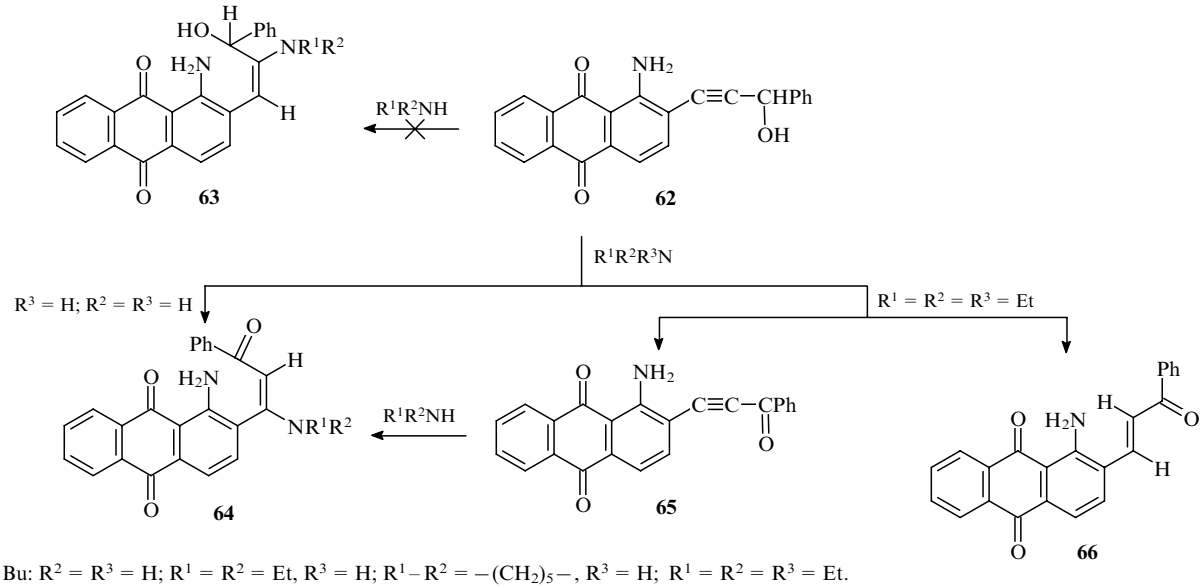
Secondary acetylenic alcohol, *viz*., 1-amino-2-(3-hydroxy-3-phenylpropynyl)anthraquinone (**62**), exhibits an unusual behaviour in reactions with amines.[27] The reactions of alcohol **62** with primary amines lead predominantly to its dehydrogenation. The reactions of alcohol **62** with secondary amines also afford dehydro adducts **64**, which are identical to products of addition of amines to 2-benzoylethynyl derivative **65** (in yields of up to 76%), rather than the expected enamino alcohols **63**. On heating with tertiary amine (Et_3N), alcohol **62** undergoes competitive dehydration to form acetylenic ketone **65** and isomerisation to vinyl ketone **66**. The mechanism of formal oxidation of the alcoholic group in compound **62** remains unclear (see Ref. 27) (Scheme 2).

Scheme 1



R^1 = H, R^2 = Bu; R^1 = R^2 = Et; R^1–R^2 = –$(CH_2)_5$–.

Scheme 2



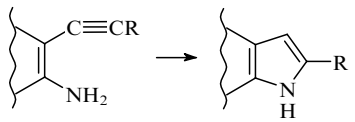
R^1 = Bu: R^2 = R^3 = H; R^1 = R^2 = Et, R^3 = H; R^1–R^2 = –$(CH_2)_5$–, R^3 = H; R^1 = R^2 = R^3 = Et.

The reactivity of amines in nucleophilic addition to alkynylanthraquinones is to a large extent determined by their spatial structure. For sterically similar amines, the reactivity increases as their basicity increases.[15]

Adducts of alkynylquinones with amines are intermediates for the synthesis of various fused heterocyclic quinoid structures.

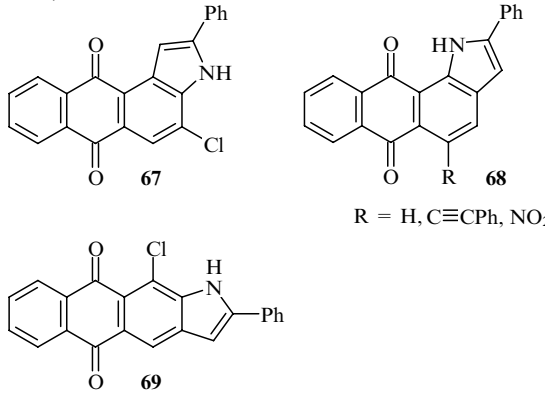
2. Pyrrole-ring closure reactions of *vic*-amino(alkynyl)quinones

It is known that in the presence of Cu(I) compounds, Pd(II) and other transition metal salts, bases or, in some cases, mineral acids, aryl- and hetarylacetylenes containing a primary or secondary amino group in the *ortho* position with respect to the acetylenic substituent undergo cyclisation to form the pyrrole ring.[59–65] This reaction was extended to vicinal acetylenic derivatives of aminoquinones.[18,21,22,29,57,66,67]



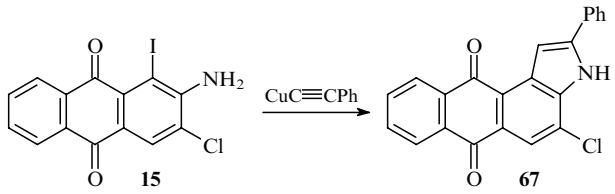
a. Catalytic cyclisation

Originally, intramolecular cyclisation of *vic*-amino(alkynyl)quinones seemed hardly possible due to low nucleophilicity of the amino group. However, it appeared that these compounds undergo intramolecular cyclisation in the presence of cuprous acetylide or powdered copper [but not Cu(I) halides] in pyridine or DMF at 80–153 °C to form the corresponding naphthoindoledione **67**–**69** with the differently fused pyrrole and anthraquinone rings (in 21%–85% yields; the reaction time is 0.5–7 h).[18,21,67]

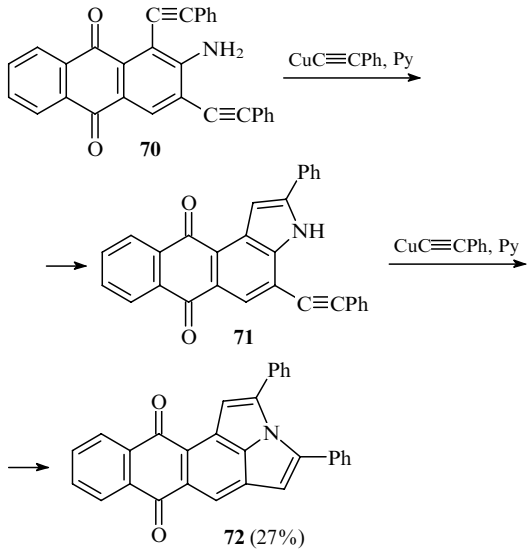


R = H, C≡CPh, NO_2

Naphthoindole **67** was prepared also in one step from *vic*-amino(iodo)anthraquinone **15** by cyclocondensation with CuC≡CPh under analogous conditions.

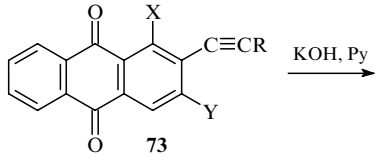


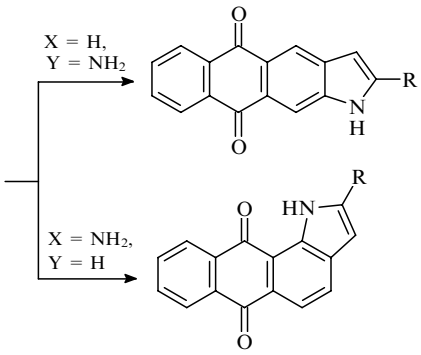
In this catalytic intramolecular reaction, like in the intermolecular addition of amines to alkynylanthraquinones, 1-alkynyl derivatives are more active. For example, 2-amino-3-chloro-1-phenylethynylanthraquinone **16** undergoes cyclisation to 2-phenylnaphtho[2,3-*e*]indole-4,9-dione (**67**) in 82% yield in pyridine in the presence of CuC≡CPh at 80 °C during 1 h, whereas isomeric 2-amino-1-chloro-3-phenylethynylanthraquinone gives 2-phenylnaphtho[2,3-*f*]indole-5,10-dione (**69**) in a yield of only 25% at 115 °C after 2 h. Under analogous conditions (80 °C, 20 min), cyclisation of 2-amino-1,3-di(phenylethynyl)anthraquinone (**70**) proceeds only involving the acetylenic substituent at position 1. In spite of the lower activity of the acetylenic group at position 3 and low nucleophilicity of the NH unit of the pyrrole ring, product **71** can undergo further cyclisation to produce 2,3-diphenylnaphtho[2,3-*e*]pyrrolo[3,2,1-*hi*]indole-6,11-dione (**72**) under more drastic conditions (115 °C, 45 h).



It is also of interest to compare the rates of cyclisation of 1-amino-2-phenylethynylanthraquinone derivatives giving rise to products **68**. Cyclisation of unsubstituted anthraquinone (R = H) was completed in 4.5 h at 115 °C (CuC≡CPh, pyridine), whereas the reaction of its nitro derivative (R = NO_2) was completed in less than 1 h at 80 °C (in spite of the fact that the nitro group should decrease the nucleophilicity of the amine thus slowing down the reaction).

It was proposed that *vic*-amino(alkynyl)anthraquinones, unlike *ortho*-alkynylanilines, can undergo cyclisation with preliminary deprotonation of the amino group under the action of bases. Solid KOH is a catalyst of choice for cyclisation of amino(alkynyl)anthraquinones **73**.[18,29]

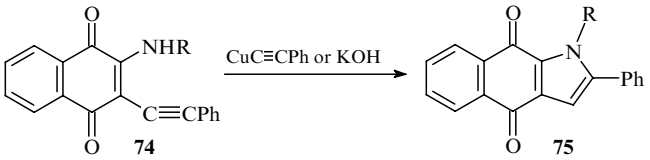




R = H, Ph; X = H, Y = NH_2; X = NH_2, Y = H.

Under these conditions, cyclisation of 1-amino-2-phenylethynylanthraquinone (**73**; R = Ph, X = NH_2, Y = H) in refluxing pyridine was completed in 15 min to give the product in 88% yield (for comparison, cyclisation of the same compound in the presence of CuC≡CPh was completed in 4.5 h, and the yield of the product was 57%). Other naphthoindolediones were prepared in 40% – 88% yields, and the reaction time was 8 – 90 min. To preclude alkaline hydrolysis, *vic*-amino(acylethynyl)anthraquinones are subjected to cyclisation with the use of K_2CO_3 in DMSO (65 – 70 °C, 10 – 20 min).[39]

Cyclisation of amino(alkynyl)-1,4-naphthoquinones **74** containing an acetylenic substituent and a secondary amino group in the quinoid ring proceeded analogously.[66] The reaction was carried out at 100 – 140 °C in pyridine, its mixture with dioxane, DMSO or mesitylene to prepare benzo[*f*]indole-4,9-diones (**75**) in 20% – 82% yields.



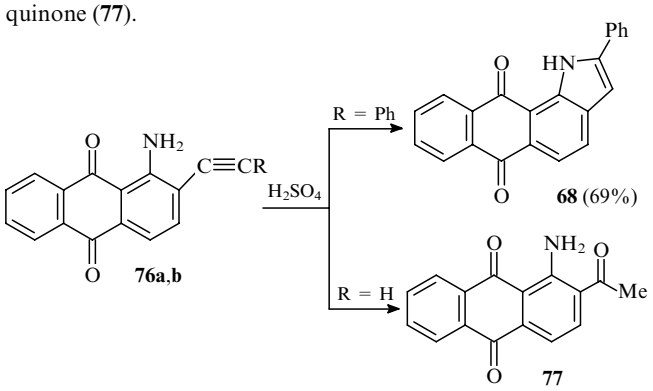
R = Me, $CH_2CH=CH_2$, $(CH_2)_2OH$, $(CH_2)_2OAc$, CH_2Ph, Ac, Ph.

Evidently, the characteristic features of cyclisation of amino(alkynyl)quinones cannot be explained only on the hypothesis that the process involves preliminary deprotonation of the amino group. It is hardly probable that the appearance of a charge on the nucleophilic centre could provide its interaction with the spatially remote β-carbon atom of the triple bond.

In the general case, the mechanism of intramolecular addition of the amino group at the triple bond catalysed by metal compounds involves the formation of a metal acetylenic π-complex and its cyclisation to a mixed organometallic compound (3-indolyl derivative), which is readily hydrolysed to the corresponding indole. Covalently bound copper from acetylide (or oxides on a copper powder surface) can be involved in stronger (compared to copper salts) dative interactions in π-complexes with a triple bond, and these interactions are additionally strengthened due to high electrophilicity of the triple bond in quinones, due to which the π-complex becomes rather stable. As a result of a change in the geometry of the triple bond in the complex, the reaction centres (the amino group and the β-carbon atom of the acetylenic substituent) are brought into proximity and the interaction between them becomes possible. Upon deprotonation of the amino group, the electrophilicity of the triple bond conjugated with this amino group decreases and the formation of a π-complex even with a proton becomes possible (for example, when KOH is used as a catalyst). This π-complex formation accompanied by a change in the geometry of the acetylenic substituent is, apparently, the necessary condition for the closure of the heterocycle.

Some acetylenic derivatives of aminoanthraquinones can undergo cyclisation to naphthoindolediones under acid cataly-

sis.[18,29] The possibility of this reaction is determined by regioselectivity of hydration of the triple bond. Actually, 1-amino-2-phenylethynylanthraquinone (**76a**) undergoes cyclisation in concentrated H_2SO_4 to form substituted naphthoindoledione **68** at 40 °C for 3 min, whereas 1-amino-2-ethynylanthraquinone **76b** gives only the hydration product, *viz*., 2-acetyl-1-aminoanthraquinone (**77**).

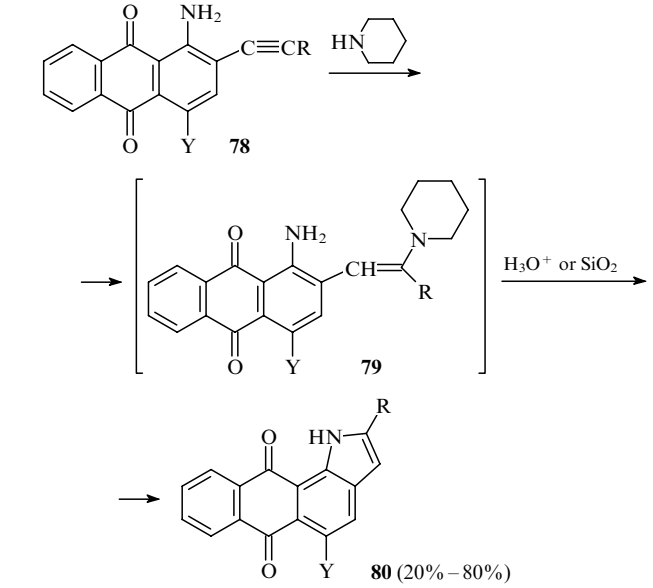


R = Ph (**a**), H (**b**).

b. Cyclisation through adducts with amines

Quinones **78** containing a vicinal primary amino group and an acetylenic substituent in the benzene ring can add secondary amines at the triple bond to form β-dialkylaminovinyl adducts **79**. Due to a change in the geometry of the unsaturated substituent (it is brought into proximity with the adjacent amino group), these adducts are easily subjected to intramolecular cyclisation in the presence of mineral acids or on SiO_2.

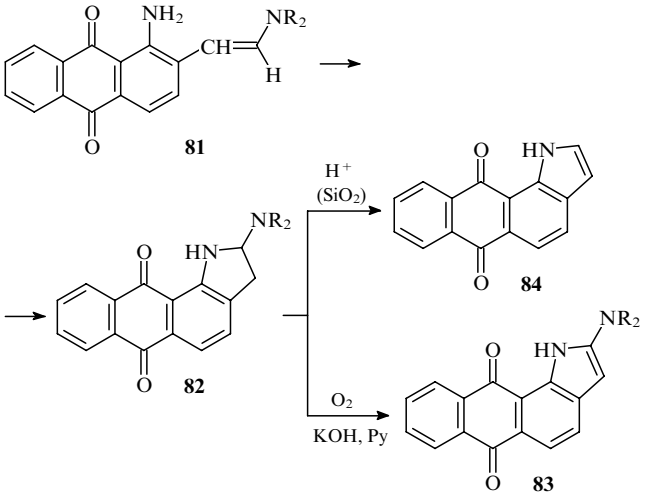
Some *vic*-amino(alkynyl)anthraquinones [for example, 1-amino-2-(3-hydroxyalk-1-ynyl)anthraquinones] are transformed into naphthoindolediones already on heating (80–105 °C) in an excess of secondary amine for several hours. The addition of amine to such acetylenes is hindered, and the resulting adducts are unstable and undergo rapid cyclisation with elimination of amine. This sequence of reactions provides the basis for a simple preparative procedure for annelation of quinones with the pyrrole ring.[18,22,27,29] This procedure was used for the synthesis of a series of naphtho[2,3-*g*]indole-6,11-diones **80**.



R = H, CH_2OH, CH(OH)Pr, CMe_2OH, CH_2OPh, CH_2N⟨O⟩;
Y = H, NO_2.

One of the possible pathways of transformations of dialkylaminovinyl derivatives of 1-aminoanthraquinone **81** into tetracyclic products involves their cyclisation to 2-dialkylamino-2,3-dihydronaphtho[2,3-*g*]indole-6,11-diones **82**, which are labile and readily undergo aromatisation with elimination of amine on silica gel or under the action of an acid.[57] The diethylaminopyrroline intermediate (R = Et) is particularly unstable: it eliminates diethylamine already under the synthesis conditions and is transformed into unsubstituted naphthoindoledione.

However, pyrroline intermediates **82** can undergo aromatisation not only through elimination of amine but also upon dehydrogenation. It appeared that these compounds underwent aromatisation with retention of the amino group at 20 °C in pyridine in the presence of KOH and atmospheric oxygen (yields were ~60%). 2-Diethylaminonaphtho[2,3-*g*]indole-6,11-dione **83** was also prepared in low yield (22%) by cyclisation of 1-amino-2-diethylaminovinylanthraquinone **81** under the same conditions. This reaction afforded unsubstituted naphthoindoledione **84** as the major product.

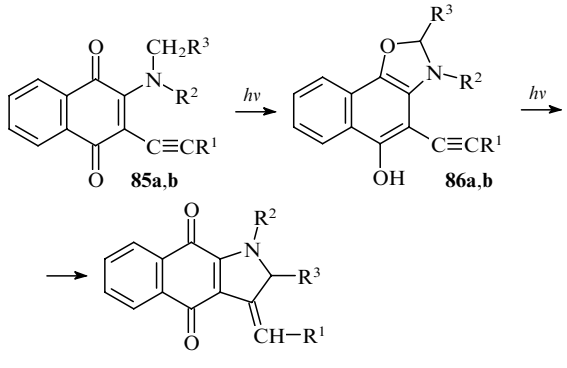


R–R = $-(CH_2)_5-$, $-(CH_2)_2O(CH_2)_2-$; R = Et.

Another pathway of cyclisation of adducts which involves hydrolysis of the dialkylaminovinyl substituent followed by the pyrrole-ring closure, is also not ruled out.

c. Photoinduced heterocyclisation

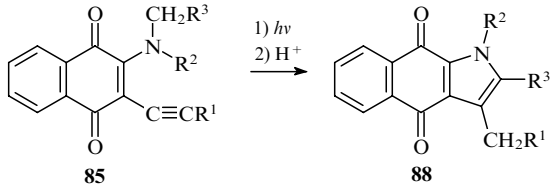
Another method for the construction of a system of fused pyrrole and quinoid rings is based on photochemical cyclisation of 3-alkynyl-2-dialkylamino-1,4-naphtho- or -1,4-benzoquinone.[68,69] This reaction involves two steps, as was exemplified by the reactions of 2-diethylamino-3-phenylethynyl- (**85a**) and 2-dimethylamino-3-(3-phenoxyprop-1-ynyl)-1,4-naphthoquinones (**85b**).[68] The first step is initiated with visible light (λ = 546 nm) and leads to the closure of the dihydrooxazole ring with the participation of the dialkylamino and vicinal carbonyl groups giving rise to intermediates **86**. On irradiation with light



R^1 = Ph, R^2 = Et, R^3 = Me (**a**); R^1 = CH_2OPh, R^2 = Me, R^3 = H (**b**).

(λ = 436 nm), the latter undergo recyclisation to the corresponding 3-alkylidene-2,3-dihydronaphtho[2,3-*b*]pyrrole-4,9-diones **87**.

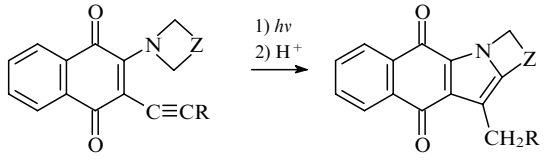
In the presence of catalytic amounts of mineral acids, photocyclisation products (compounds **87**) are isomerised into substituted naphtho[2,3-*b*]pyrrole-4,9-diones **88**.[69] The latter can be synthesised from alkynylquinones without isolation of intermediate dihydroindolequinones.



85 **88**

R^1 = H, CH_2OPh, Ph; R^2 = Me, Et; R^3 = H, Me.

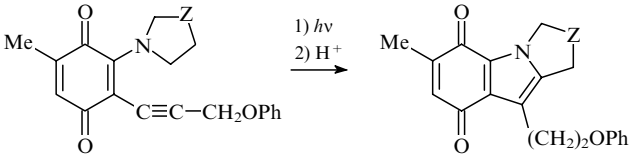
If the dialkylamino group in the starting alkynylquinone **89** is a residue of cyclic amine, photocyclisation affords tetracyclic heterocyclic quinones **90**.[69]



89 **90** (16% – 60%)

Z = $-(CH_2)_2-$, $-(CH_2)_3-$, $-CH_2OCH_2-$; R = Ph, CH_2OPh.

Analogously, tricyclic compounds **92** are derived from 3-alkynyl-2-amino-1,4-benzoquinones **91**.



91 **92**

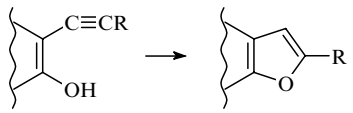
Z = $-CH_2-$, $-(CH_2)_2-$.

Quinones bearing a nitrogen atom at the fusion of two rings are structurally similar to natural antitumour antibiotics of the mitomycin family.

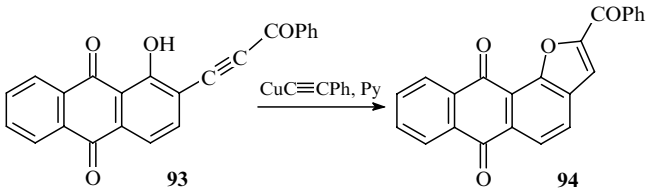
3. Furan-ring closure reaction

a. Reactions of *vic*-hydroxy(alkynyl)quinones

vic-Acetylenic derivatives of hydroxyanthraquinones (like *ortho*-hydroxyarylacetylenes[60,70–72]) undergo cyclisation in the presence of copper or palladium catalysts or bases to form the furan ring. Generally, the reactions proceed under mild conditions and give products in good yields.

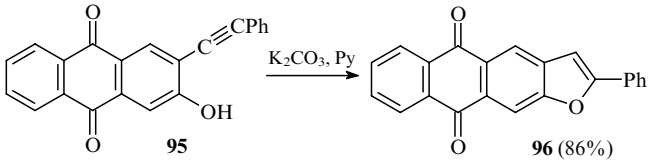


For example, 1-hydroxy-2-benzoylethynylanthraquinone (**93**) undergoes cyclisation under the action of CuC≡CPh in pyridine already at 20 °C during 30 min. Although the presence of the carbonyl group in the acetylenic substituent of quinone should hinder the attack of the nucleophile at the adjacent carbon atom, the yield of 2-benzoylanthra[1,2-*b*]furan-6,11-dione (**94**) amounts to 68%.[39]



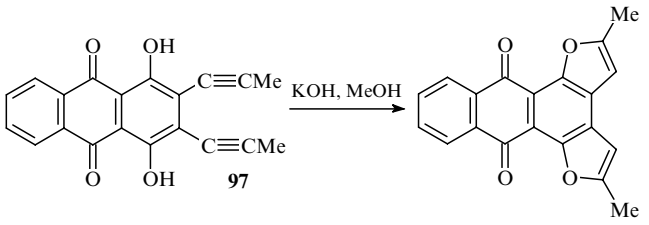
93 **94**

In the presence of solid K_2CO_3, 2-hydroxy-3-phenylethynylanthraquinone **95** undergoes cyclisation in refluxing pyridine to give 2-phenylanthra[2,3-*b*]furan-5,10-dione **96** during 3 min.[69]



95 **96** (86%)

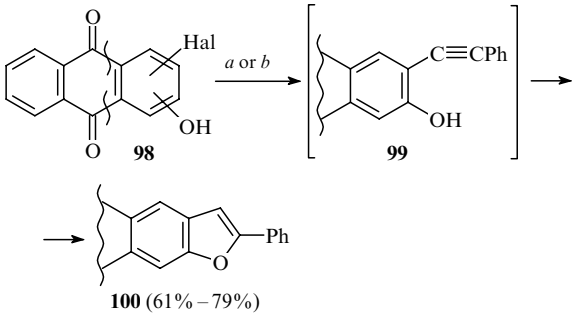
Cyclisation of 1,4-dihydroxy-2,3-di(prop-1-ynyl)anthraquinone (**97**) in a refluxing 1.5% KOH solution in MeOH proceed much more slowly; the conversion is approximately 90% after 24 h.[52]



97

The mechanism of this heterocyclisation under various conditions was not studied in detail. However, this mechanism is, apparently, similar to that of the pyrrole-ring closure (see Section III.2.a).

Cross-coupling of *vic*-hydroxy(iodo)anthraquinones (**98**, Hal = I) both with cuprous acetylides[38,69] and terminal acetylenes catalysed by palladium complexes[17,69] affords directly anthrafurandiones. Unlike condensation of *vic*-amino iodides, the replacement of the halogen atom in this reaction is the rate-determining step and the expected acetylenic intermediates of the reaction (compounds of type **99**) are not detected. Stable cuprous acetylides (for example, CuC≡CPh) have proved themselves in the synthesis of anthrafurandiones. For instance, the reaction time of cyclocondensation at 20–115 °C is only 5–10 min.[38,69] This method was used for the synthesis of all three isomeric anthrafurandiones (**100**).



98 **99**

100 (61% – 79%)

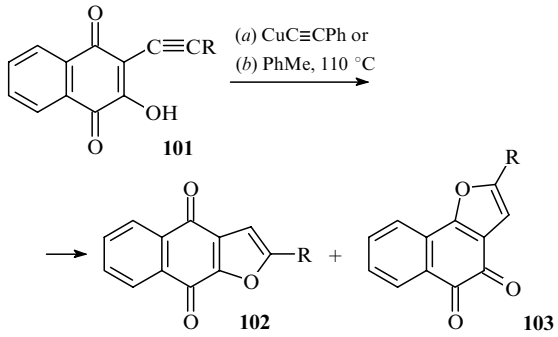
Hal = I, Br;
(*a*) CuC≡CPh; (*b*) HC≡CPh, $Pd(PPh_3)_2Cl_2$, CuI, K_2CO_3, Py.

2-Hydroxy-1-iodoanthraquinone is most reactive in this reaction. In this case, cross-coupling is completed in the above-mentioned time at room temperature. The reactivity of the corresponding bromide is also high. For example, its condensation with CuC≡CPh is completed in 5 min at 115 °C. The reaction of 1-chloro-2-hydroxyanthraquinone virtually does not proceed.

Catalytic cross-coupling of *vic*-hydroxy(iodo)anthraquinones with terminal acetylenes has some advantages over acetylide condensation, because it allows one to use alkynes, which do not form stable acetylides (aminopropynes, acetylenic alcohols, *etc*.). Catalytic cyclocondensation was carried out for different isomers of *vic*-hydroxy(iodo)anthraquinones (the yields were 34% – 80%).[17, 69]

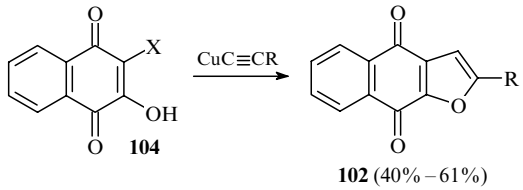
1,4-Naphthoquinones **101** containing the hydroxy and acetylenic groups in the quinoid ring undergo intramolecular cyclisation in the presence of CuC≡CPh under very mild conditions (pyridine – dioxane, 20 °C, 3 – 5 min) [69] to give the expected linear heterocyclic *para*-quinones **102** along with their isomers, *viz*., angularly fused *ortho*-quinones **103**.

2-Alkynyl-3-hydroxy-1,4-naphthoquinones can undergo cyclisation with the closure of the furan ring in the absence of catalysts as well.[69] At 110 °C, compounds **101** in toluene also give mixtures of heterocyclic *para*- and *ortho*-quinones, but in another ratio.



R	Reaction conditions	Yield (%)	
		102	**103**
Ph	*a*	59	16
	b	10	84
C_8H_{17}	*a*	23	6
	b	24	74

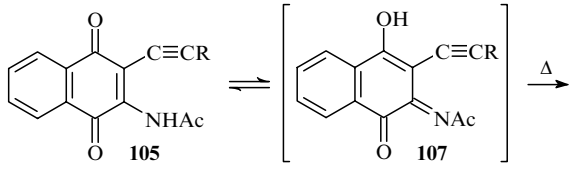
However, cyclocondensation of 2-halogeno-3-hydroxy-1,4-naphthoquinones **104** with Cu(I) acetylides at 100 °C proceeds regioselectively to form linear naphtho[2,3-*b*]furan-4,9-diones **102**.

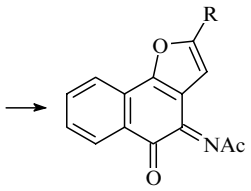


X = I, Br; R = Bu, C_8H_{17}, CH_2OMe, Ph.

b. Other reactions of the furan-ring closure

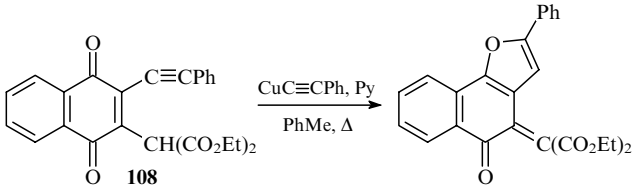
Angular annelation of the quinoid moiety with the furan ring occurred upon thermal cyclisation of 3-acetylamino-2-alkynyl-1,4-naphthoquinones **105**.[66]





R = CMe_2OH, Ph.

The formation of products **106** can be attributed to the transformation of tautomer **107**. Actually, this cyclisation becomes impossible upon the replacement of the *N*-acetyl group by the *N*-alkyl group. Angular heterocyclisation is, apparently, associated with the acidic properties of the acetylamino group and, hence, structurally similar CH acids are also able to undergo this cyclisation. For example, malonic acid derivative **108** was transformed into naphthofuran **109** by heating in toluene in the presence of small amounts of CuC≡CPh and pyridine.[69]

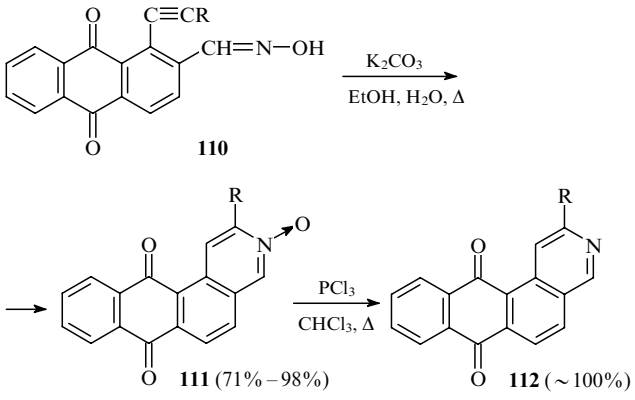


4. Pyridine-ring closure reactions

Intramolecular cyclisation of quinones bearing an acetylenic substituent and a nitrogen-containing group in the adjacent positions of the aromatic ring can be used for their annelation with the pyridine ring. Depending on the structures of the substituents involved in the formation of the heterocycle, the products contain either the quinoline or isoquinoline fragment.

a. Cyclisation of *vic*-alkynylanthraquinone aldoximes

1-Alkynylanthraquinone-2-aldoximes **110** are transformed into 2-substituted naphtho[2,3-*f*]isoquinoline-7,12-dione *N*-oxides **111** by refluxing in 90% aqueous EtOH in the presence of K_2CO_3 for 15 min. Compounds **111** can be reduced to the corresponding naphthoisoquinolinediones **112**.[35]



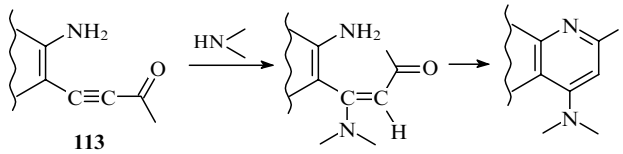
R = Bu, CH_2OPh, Ph.

This cyclisation was carried out also for analogous derivatives of indole,[73] benzene [64, 74] and pyridine.[64, 75]

b. Cyclisation of *vic*-amino(acylethynyl)- and *vic*-amino(ethoxycarbonylethynyl)anthraquinones

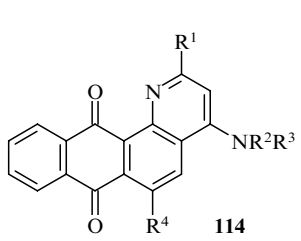
Another method for the construction of the anthrapyridine structure is based on the use of *vic*-acylethynyl derivatives of aminoanthraquinones **113**. This method involves the nucleophilic addition of amines (secondary or primary) at the activated triple

bond of the starting compound followed by intramolecular cyclisation of the adduct with the participation of the carbonyl group of the side chain and the aromatic amino group.[36, 58] The role of the amine addend consists, primarily, of changing the geometry of the unsaturated substituent resulting in a close arrangement of the reacting fragments, which is necessary for the closure of the heterocycle. In this case, the *Z* configuration of the adduct is reactive. The amino group introduced is retained in the newly formed pyridine ring.

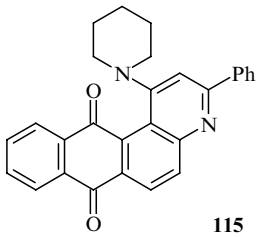


113

Substituted naphtho[2,3-*h*]quinoline-7,12-diones (**114**), naphtho[2,3-*f*]quinoline-7,12-dione (**115**) and naphtho[2,3-*g*]quinoline-6,11-dione (**116**) were synthesised by cyclisation of 2-acylethynyl-1-amino-, 1-acylethynyl-2-amino- and 3-acylethynyl-2-aminoanthraquinones, respectively.

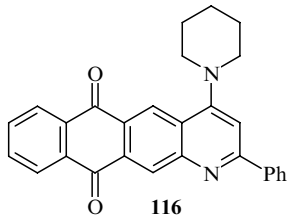


114



115

R^1 = Bu^t, Ph; R^2 = H, Et, R^3 = Et, Bu, C_8H_{17}; R^2-R^3 = $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_2O(CH_2)_2-$; R^4 = H, Cl, NO_2.



116

Cyclisation of adducts is carried out at room temperature (by shaking benzene solutions with dilute HCl over a short period of time or stirring with KOH in pyridine) or at 80 °C in the presence of $POCl_3$. In some cases, cyclisation proceeds already under the conditions of the preparation of the adduct (heating of acetylenic ketone **113** in an excess of amine). The rate of cyclisation depends on the structure of the adducts. Under alkaline conditions, the time of cyclisation of amino adducts of 1-amino-2-benzoylethynylanthraquinone is 5–15 min, whereas the time of cyclisation of the adduct of 2-amino-1-benzoylethynyl-3-chloroanthraquinone with piperidine is as large as 2 h due, apparently, to steric hindrance. Cyclisation of (monoalkylamino)vinyl ketones under the action of acids is more difficult to perform compared to that of analogous (dialkylamino)vinyl ketones. The yields of mono- and dialkylaminonaphthoquinolinediones in both acidic and basic media are in the range of 54%–100%.

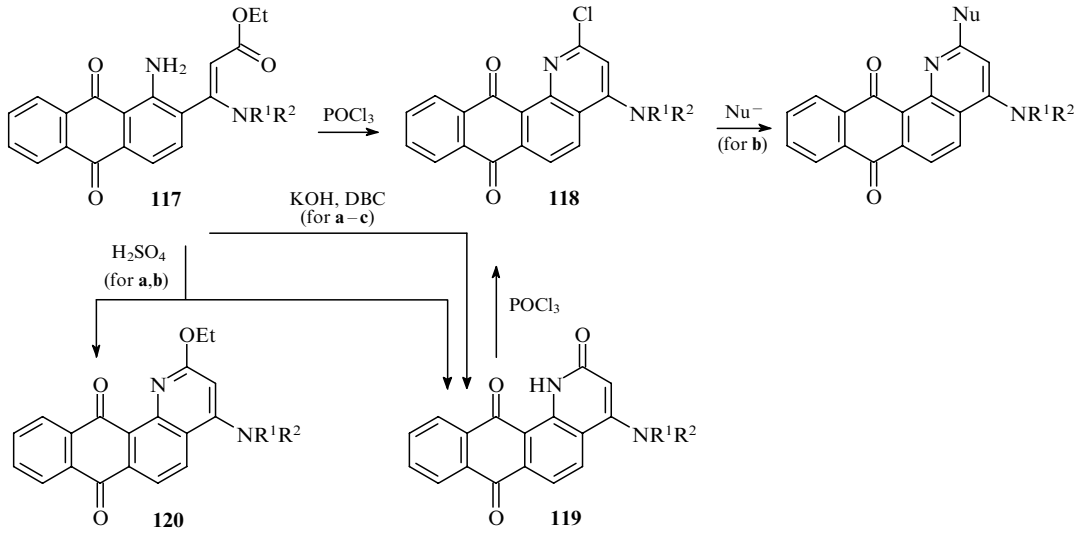
Modified version of this method was used for the preparation of 4-aminonaphtho[2,3-*h*]quinoline-7,12-diones containing functional substituents at position 2.[25, 26] In this case, esters **117** rather than aminovinyl ketones are subjected to cyclisation (Scheme 3).

These compounds are transformed into 2-chloro-substituted 4-aminonaphthoquinolinediones **118** (in 41%–67% yields) under the action of $POCl_3$ in dioxane at 80 °C. The nucleophilic substitution of the labile halogen atom in the pyridine ring allows one to perform further modifications of the molecule.

The same 4-amino-2-chloronaphtho[2,3-*h*]quinoline-7,12-diones **118** can be prepared from esters **117** in two steps through δ-lactams (naphthoquinolinetriones **119**). The closure of the lactam ring in adducts **117** proceeds readily in the presence of solid KOH and dibenzo-18-crown-6 in benzene at 20 °C (the yields are 92%–97%). Under conditions of acid catalysis (H_2SO_4, benzene, 20 °C), adducts **117** give mixtures of lactams **119** and 4-amino-2-ethoxynaphthoquinolinediones **120** in a ratio of ~2 : 1. Naphthoquinolinetriones **119** are transformed into compounds **118** (in 67%–98% yields) by heating with $POCl_3$ in dioxane.

It should be noted that catalytic hydrogenation of secondary (1-aminoanthraquinon-2-yl)alk-1-yn-3-ols giving rise to *cis*-ethylenic alcohols and subsequent oxidation of the latter with MnO_2 or $CrO_3 \cdot 2\,Py$ can be used for the synthesis of naphtho[2,3-*h*]quinoline-7,12-diones, which are structurally analogous to compounds **114** but are devoid of the alkynylated amino group in the pyridine ring.[27] Naphthoquinolinediones **114** form chelate complexes with metal halides (Cr, Mn, Co, Cu, Ga, Zn, Pd, In or Ni) in which the nitrogen atoms of the heterocycle and the oxygen atom of the carbonyl group at position 12 are involved in coordination.[76] 4-Monoalkylamino derivatives **114** (R^3 = H) are involved in complexes as amino tautomers. Some aminonaphthoquinolinediones exhibit high cytotoxic activity with respect to malignant cells.[39, 77]

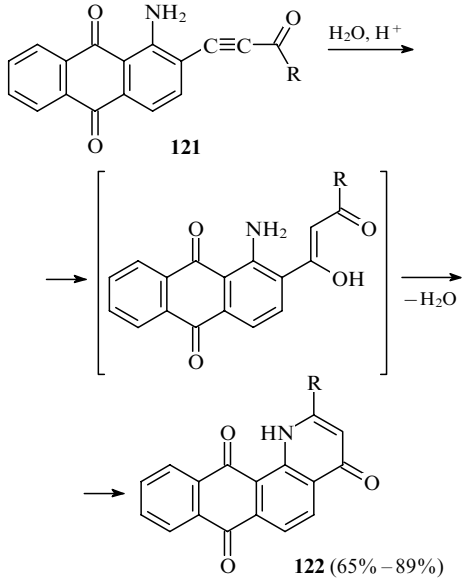
Scheme 3



R^1 = R^2 = Et (**a**), R^1-R^2 = $-(CH_2)_5-$ (**b**); R^1 = H, R^2 = Bu (**c**); Nu = pip, SBu, $CH(CO_2Et)_2$; DBC is dibenzo-18-crown-6.

The above-considered method for heterocyclisation of acetylenic ketones through amino adducts is not specific only for anthraquinone derivatives.[36]

Under conditions of hydration of the triple bond, *vic*-amino(acylethynyl)anthraquinones **121** are subjected to cycloisomerisation to naphthoquinolinetriones **122**.[39,78,79] The reaction proceeds according to a scheme analogous to that of the formation of the aminonaphthoquinoline system under acidic conditions. Initially, water adds at the triple bond and then it is eliminated upon the closure of the heterocycle. Heterocyclisation is carried out either in concentrated H_2SO_4 at 75–85 °C or in the presence of $HgSO_4$ and a small amount of 50% H_2SO_4 by refluxing in dioxane.



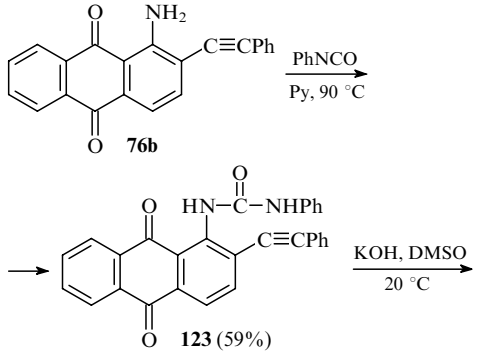
R = Bu^t, Ph.

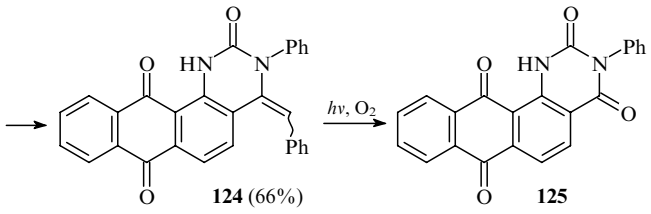
Spectroscopic and quantum-chemical study of the structure of 1*H*-2-phenylnaphtho[2,3-*h*]quinoline-4,7,12-trione (**122**, R = Ph) demonstrated that this compound exists in the polarised quinolone form stabilised by an intramolecular hydrogen bond in both the crystalline state and solutions.[79]

Naphthoquinolinetriones **122** form labile complexes with Lewis acids ($GaCl_3$, $CoCl_2$, $MnCl_2$ or $CuCl_2$) in which the ligand is coordinated to the metal atom through the oxygen atom of pyridone.[80] Protonation of triones **122** also proceeds at this atom.[79]

5. Cyclisation with the pyrimidine-ring closure

N-(2-Phenylethynylanthraquinon-1-yl)-*N*′-phenylurea (**123**), which was prepared by the reaction of the corresponding amino(alkynyl)anthraquinone **76b** with PhNCO, underwent cyclisation to 1*H*-4-benzylidene-3-phenylnaphtho[2,3-*h*]quinazoline-2,7,12-trione (**124**) in the presence of KOH in aqueous DMSO.[81]





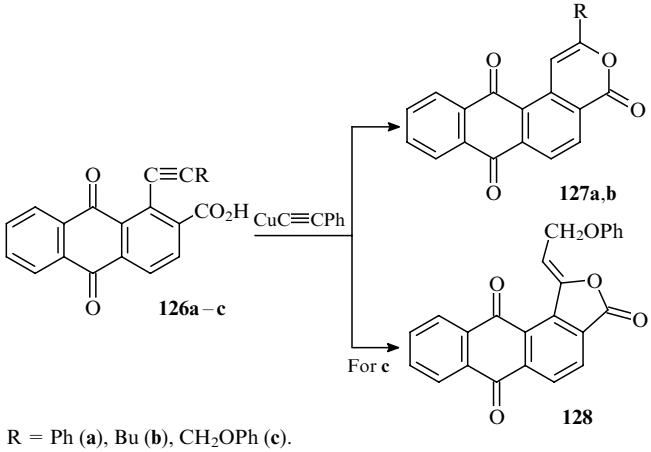
Product **124** was prepared as a mixture of *E* and *Z* isomers (in a ratio of 7 : 2). Upon photolysis (on SiO_2 or in solutions), the isomers are oxidised with atmospheric oxygen to 1*H*-3-phenylnaphtho[2,3-*h*]quinazoline-2,4,7,12-tetrone (**125**).

6. Pyrone-ring closure reactions

a. Reactions of *vic*-alkynylanthraquinonecarboxylic acids

In the presence of Cu(I) compounds, *vic*-acetylenic derivatives of anthraquinonecarboxylic acids (like those of other aromatic carboxylic acids) undergo cyclisation to give lactones. In these reactions, the closure of the γ- or δ-lactone rings (5-*exo*-dig or 6-*endo*-dig addition, respectively) can take place. 1-Alkynylanthraquinone-2-carboxylic acids form lactones in the presence of CuC≡CPh (pyridine, 20 °C, 77%–91% yields).[19] However, Cu-catalysed cyclisations of anthraquinonecarboxylic and parent benzoic acids follow different pathways. Thus anthraquinonecarboxylic acids have a tendency for 6-*endo*-dig addition (to form δ-lactones), whereas 5-*exo*-dig addition (giving rise to γ-lactones) is more typical of benzoic acids.[60,82]

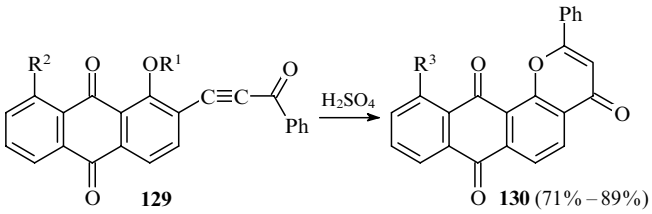
1-Phenylethynyl- (**126a**) and hex-1-ynylanthraquinone-2-carboxylic acids (**126b**) give exclusively δ-lactones **127**, and only 1-(3-phenoxyprop-1-ynyl)-substituted acid (**126c**) forms a mixture of γ- and δ-lactones (**127** and **128**) in a ratio of 4 : 3.



R = Ph (**a**), Bu (**b**), CH_2OPh (**c**).

b. Reactions of *vic*-acylethynyl(hydroxy)anthraquinones

The synthesis of anthra[1,2-*b*]pyran-4,7,12-triones attracts interest because this fused system represents a cyclic moiety of natural antitumour antibiotics of the kidamycin group[83–85] and their biologically active analogues prepared by biochemical methods.[86–88] 2-Acylethynyl-1-hydroxyanthraquinones (**129**, R^1 = H) serve as convenient precursors for the synthesis of these compounds. The simplest pathway of transformations of these compounds into target products **130** involves cyclisation under conditions of hydration of the triple bond.[39] The reaction proceeds readily in concentrated H_2SO_4 at 70–80 °C and is completed in 0.5–1.5 h. *O*-Acyl-substituted derivatives **129** (R^1 = COPh) can also be used in the synthesis.

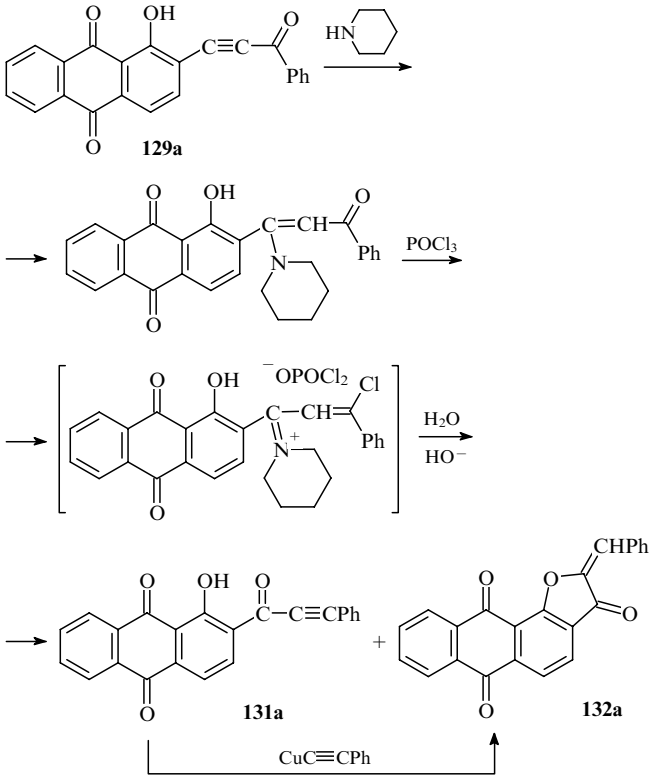


129 **130** (71% – 89%)

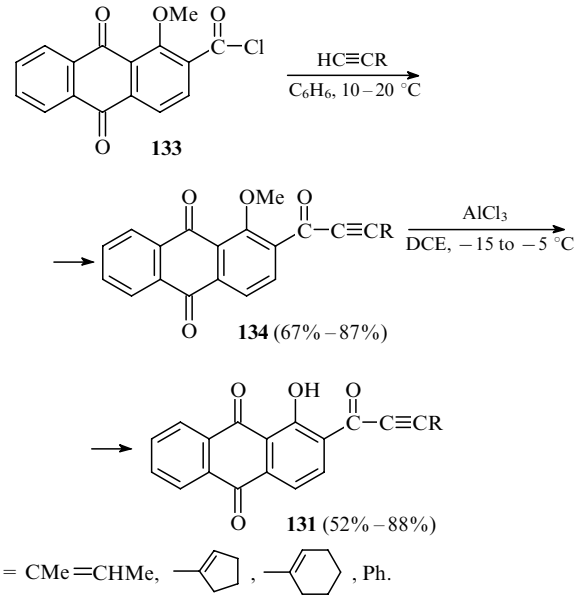
R^1 = H, PhCO; R^2 = H, OH, OAc; R^3 = H, OH.

Unfortunately, this procedure for the closure of the γ-pyrone ring is unsuitable for compounds containing acid-sensitive groups. Besides, kidamycin antibiotics contain unsaturated or epoxide fragments at position 2 of the anthrapyran moiety, which precludes the use of strongly acidic media in the synthesis of the starting compounds. However, under other conditions, the starting acetylenic ketones are more prone to cyclisation giving rise to a five-membered rather than a six-membered heterocycle.

It was expected that the use of alkynyl anthraquinonyl ketones **131a** as the starting compounds would facilitate the formation of the γ-pyrone ring and make it possible to perform cyclisation under rather mild conditions. In this connection, let us mention an attempt to prepare ketone **131a** by isomerisation of ketone **129a**.[39, 89, 90] Unfortunately, this isomerisation is accompanied by partial cyclisation of compound **131a** to isomeric furanone **132a**, which is also generated from **131a** by heating with CuC≡CPh in toluene at 90 °C.[39]



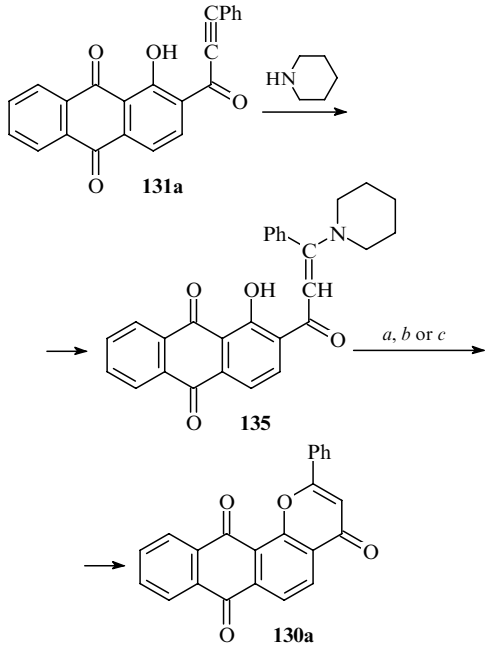
An alternative method for the synthesis of alkynyl hydroxyanthraquinonyl ketones **131** involves catalytic acylation of terminal acetylenes with 1-methoxyanthraquinone-2-carboxylic acid chloride (**133**) in the presence of $Pd(PPh_3)_2Cl_2$, CuI and Et_3N followed by removal of the methyl protective group.[91] Due to the presence of the carbonyl group in the *ortho* position, methoxy ketones **134**[92] are demethylated with Lewis acids under exceptionally mild conditions (dichloroethane, from −15 to −5 °C).



R = CMe=CHMe, , , Ph.

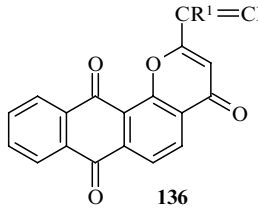
To develop a general procedure for cyclisation applicable to labile highly unsaturated hydroxy ketones, the transformation of 1-hydroxy-2-(1-oxo-3-phenylpropynyl)anthraquinone **131a** into phenylanthrapyrantrione **130a** was studied under various conditions.[39]

Evidently, in order for the desired six-membered ring to be formed, the oxygen atom of the hydroxy group and the γ-carbon atom of the acetylenic substituent must be brought into proximity, which is achieved by the attachment of secondary amine (for example, of piperidine) at the triple bond of the starting ketone. The resulting adduct **135** undergoes cyclisation with the closure of the γ-pyrone ring both under conditions of acid hydrolysis and base-catalysed intramolecular nucleophilic substitution of a secondary amino group. However, cyclisation of adduct **135** on SiO_2 as an adsorbent (82% yield) provides the formation of 2-phenylanthra[1,2-*b*]pyran-4,7,12-trione (**130a**) under the most mild conditions.



(*a*) H_2SO_4, $CHCl_3$ – dioxane – H_2O, 80 °C; (*b*) pip, C_6H_6, 80 °C; (*c*) SiO_2, $CHCl_3$.

This procedure was successfully extended to hydroxyanthraquinonyl vinylethynyl ketones[91] and opened the way to the synthesis of anthra[1,2-*b*]pyran-4,7,12-trione derivatives **136** containing unsaturated substituents at position 2.



136

$R^1 = R^2 = Me$; $R^1 - R^2 = -(CH_2)_3-$, $-(CH_2)_4$.

7. Reactions with hydrazine

a. Cyclocondensation of *peri*-acetylenic derivatives of anthraquinone and naphthoquinone

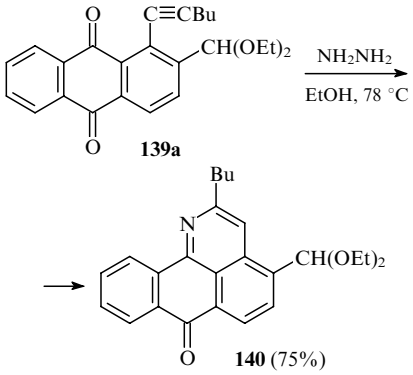
1-Alkynylanthraquinones **11** react with hydrazine or hydrazine hydrate to form mixtures of substituted 4*H*-anthra[9,1-*cd*]-1,2-diazepin-8-one (diazepineanthrone **137**) and 7*H*-dibenzo[*de*,*h*]-quinolin-7-one (pyridineanthrone **138**), which are easily separated by chromatography (Scheme 4).[23, 93, 94]

Prolonged heating of diazepineanthrones **137** in pyridine in the presence of NH_2NH_2 leads to reductive elimination of one nitrogen atom from the seven-membered heterocycle giving rise to pyridineanthrones **138**. For example, the reaction of the compound with R = Ph is completed in 9 h at 115 °C (78% yield). This transformation occurs already under the conditions of cyclocondensation, and, hence, an increase in the reaction time leads to an increase in the percentage of pyridineanthrones **138** in a mixture of reaction products.

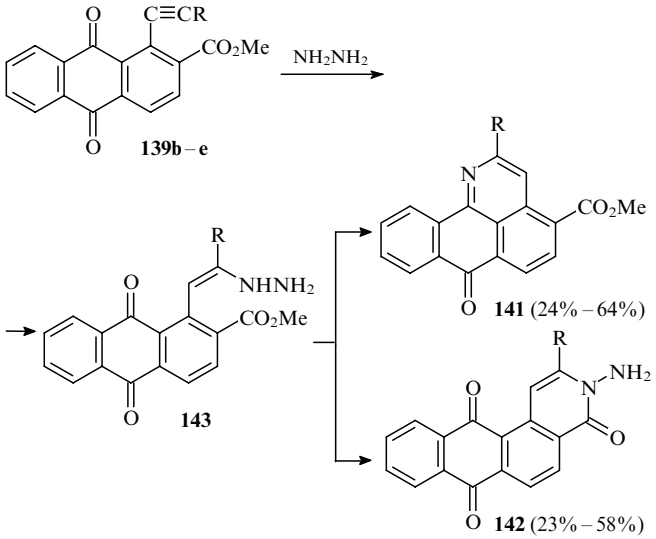
It is assumed that the mechanism of the seven-membered ring contraction involves hydration, ring opening and recyclisation to a six-membered ring followed by reduction with an excess of NH_2NH_2. The reduction step, unlike other steps, is irreversible.

Bulky substituents at position 2 of the starting alkynylanthraquinones hinder the formation of a seven-membered heterocycle. For example, fused pyridine derivative **140** is the only product generated from 1-(hex-1-ynyl)-2-diethoxymethylanthraquinone (**139a**).

In the presence of an alkoxycarbonyl substituent at position 2 (compounds **139b**–**e**), the reaction with hydrazine affords a mixture of substituted pyridineanthrone **141** and *N*-aminolactam **142**.[37, 93, 94] Apparently, the electron-withdrawing alkoxycarbonyl group enhances the reactivity of the acetylenic fragment and the reaction in refluxing EtOH is completed in 2–90 min (total yields are 72%–87%).



139a → **140** (75%)

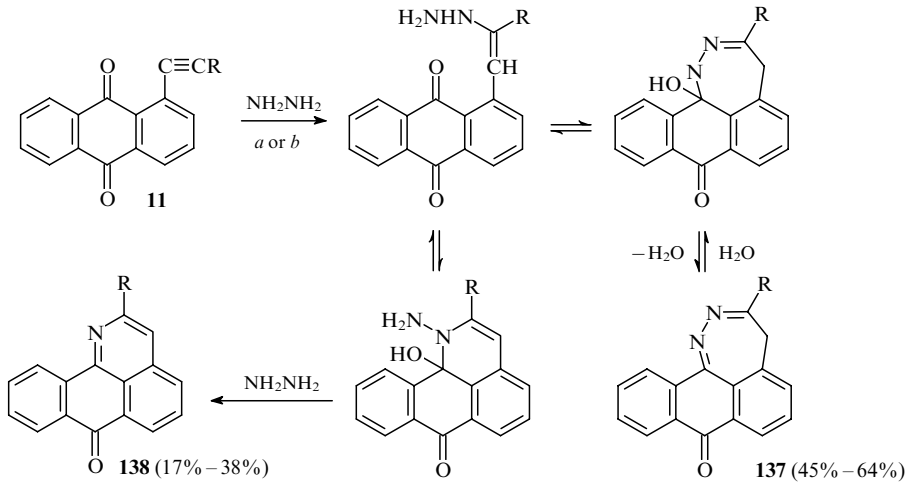


139b–**e** → **141** (24%–64%) + **142** (23%–58%) via **143**

R = H (**b**), Bu (**c**), CH_2OPh (**d**), Ph (**e**).

Investigation of the mechanism of formation of *N*-aminolactams **142** demonstrated that the reaction proceeds through adduct **143** as the intermediate. A comparison of the times of condensation of various acetylenic esters as well as the ratios between the reaction products showed that the formation of lactams through this adduct is the major pathway. It should be noted that cyclisation of *ortho*-alkynylbenzoic acid hydrazides proceeds with the closure of the γ-lactam ring.[95] Apparently, this difference is additional evidence for the fact that adducts **143**

Scheme 4

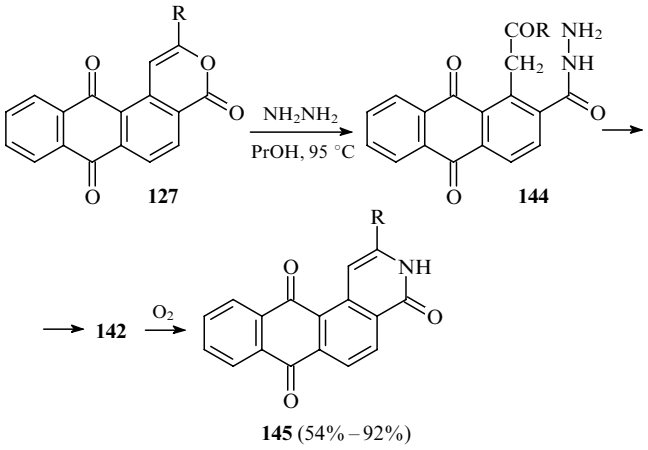


11 → **138** (17%–38%) + **137** (45%–64%)

R = Bu, Ph, CMe_2OH, CH_2OPh. (*a*) Py, 90–115 °C, 20–90 min; (*b*) EtOH, 78 °C, 10 h.

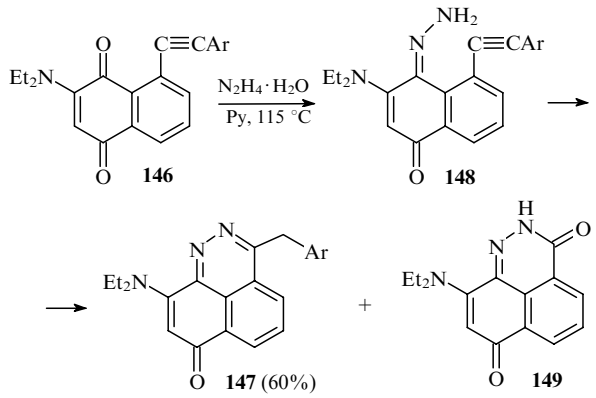
rather than acid hydrazides are initially generated in the course of cyclocondensation of compounds **139**.

N-Aminolactams **142** can also be prepared by hydrazinolysis of the corresponding lactones **127**.[37] The reaction involves the opening of the lactone ring to form labile 1-(2-oxoalkyl)anthraquinone-2-carboxylic acid hydrazides **144**, which undergo subsequent cyclisation. Deamination of aminolactams **142** under the action of oxygen in the presence of CuCl affords δ-lactams **145**.



R = Bu, Ph.

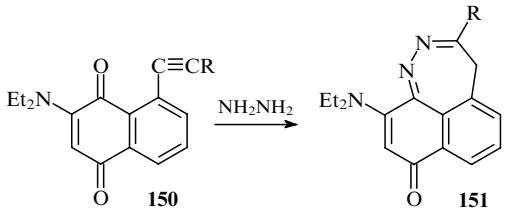
Condensation of *peri*-acetylenic derivatives of 1,4-naphthoquinone with NH_2NH_2 follows a pathway which differs from that of *peri*-alkynylanthraquinones. For example, the reaction of 3-diethylamino-5-phenylethynyl-1,4-naphthoquinone (**146**, Ar = Ph) with an excess of $NH_2NH_2 \cdot H_2O$ in pyridine is accompanied by the closure of the pyridazine rather than the diazepine ring to form 3-benzyl-9-diethylaminobenzo[*de*]cinnolin-7-one (**147**) in 67% yield.[28,96]

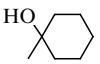
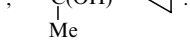


Ar = Ph, 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$.

This pathway of cyclocondensation of *peri*-arylethynyl-1,4-naphthoquinones is attributable to the initial formation of hydrazone **148**, which undergoes subsequent cyclisation. This reaction is sensitive to the structure of the starting compound. For example, the introduction of the electron-donating methoxy group at the *para* position of the benzene ring of the acetylenic substituent (Ar = 4-$MeOC_6H_4$) leads to a substantial increase in the reaction time (from 8 to 35 h). In this case, the reaction mixture undergoes substantial resinification and the yield of the product sharply decreases. By contrast, the reaction with a compound containing the electron-withdrawing nitro group (Ar = 4-$O_2NC_6H_4$) proceeds vigorously and is completed in 1 – 3 min. In addition, the nitro group in the starting acetylene serves as an internal oxidiser, as a result of which compound **149**, which was generated due to oxidative elimination of the benzyl fragment, rather than the expected benzocinnolinone **147** (Ar = 4-$NO_2C_6H_4$) was obtained as the major product (the yields were 34% and 19%, respectively).

The replacement of the arylethynyl substituent in *peri*-alkynyl-1,4-naphthoquinones by a γ-hydroxyalkynyl group changes the regioselectivity of condensation.[28,97] Under the same conditions, the reactions of 3-diethylamino-5-(3-hydroxyalkyn-1-yl)-1,4-naphthoquinones **150** with $NH_2NH_2 \cdot H_2O$, unlike those of 5-arylethynyl derivatives **146**, lead to the closure of the seven-membered diazepine ring (analogously to the reactions of *peri*-alkynylanthraquinones).

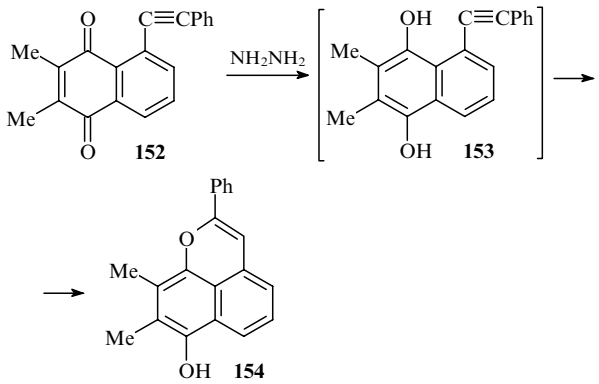


R = CMe_2OH, , 

The reactions are completed in 5 – 6 h and are accompanied by noticeable resinification. Nevertheless, the preparative yields of substituted 4*H*-naphtho[1,8-*cd*]-1,2-diazepin-8-ones **151** are as high as 53% – 56%.

It is assumed that the direction of cyclisation changes due to association of the hydroxy group of the substrate with hydrazine *via* hydrogen bonds. As a result, the first step of condensation involves the addition of NH_2NH_2 at the triple bond rather than at the carbonyl group.

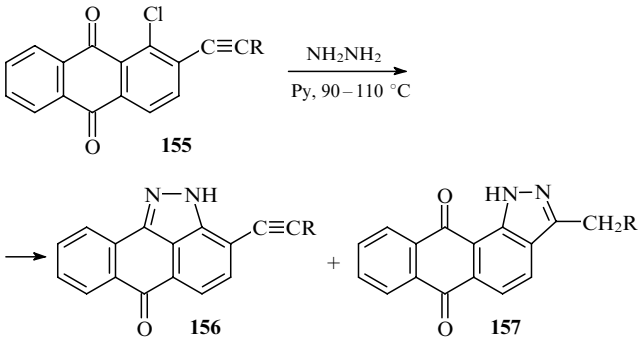
It should be noted that the nature of substituents in the quinoid ring of *peri*-alkynyl-1,4-naphthoquinones can also substantially influence the direction of their reactions with NH_2NH_2. For instance, the reaction of 2,3-dimethyl-5-phenylethynyl-1,4-naphthoquinone (**152**) involves reduction to the corresponding hydroquinone **153**, which undergoes subsequent cyclisation to give naphthopyran derivative **154**.[96]



b. Cyclocondensation of 2-alkynyl-1-chloroanthraquinones

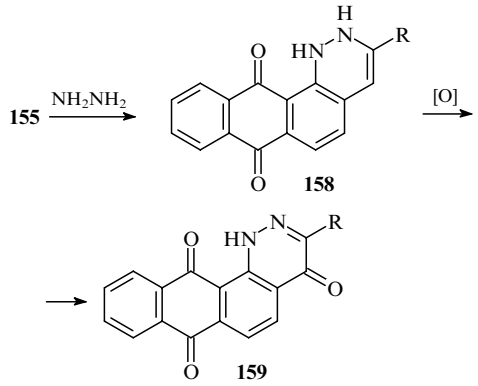
Several studies were devoted to cyclocondensation of aryl- and hetarylacetylenes containing the labile chlorine atom in the *ortho* position with hydrazine and its derivatives.[98 – 101] The reaction starts, apparently, with the replacement of the halogen atom[99] and always gives rise to a five-membered heterocyclic compound, *viz*., a derivative of pyrazole or *N*-substituted pyrrole.

2-Alkynyl-1-chloroanthraquinones **155**, in which the halogen atom has high nucleofugic lability, are readily condensed with NH_2NH_2 on heating in pyridine.[94,97] Under these conditions, the reactions of quinones bearing hydrocarbon (Alk or Ar) acetylenic substituents can follow two pathways with the pyrazole-ring closure involving either the carbonyl group of the quinoid ring (compound **156**) or the triple bond (compound **157**). The regioselectivity of the reaction depends on the nature of the substituent in the starting alkynylquinone.



R	Yield (%)	
	156	**157**
Ph	44	22
C_5H_{11}	45	–

The introduction of the hydroxy or methoxy group at the γ position of the acetylenic substituent changes the regioselectivity of cyclocondensation. In this case, the reaction affords a compound containing the six-membered dihydropyridazine ring, *viz*., substituted 1,2-dihydronaphtho[2,3-*h*]cinnoline-7,12-dione (**158**), as the only product, which is readily oxidised with oxygen to give 1*H*-naphtho[2,3-*h*]cinnoline-4,7,12-trione (**159**).

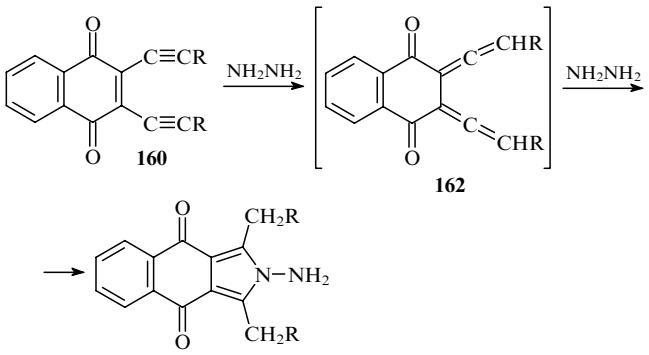


R = CH_2OH, $CH(OH)Pr^i$, CMe_2OH, $C(OMe)Me_2$.

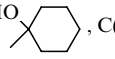
A preparative one-pot procedure was developed for the synthesis of naphthocinnolinetriones **159** from alkynylquinones **155** with the use of 25% – 30% H_2O_2 as an oxidising agent, which is added to the reaction mixture after completion of cyclocondensation (20 – 40 °C, yields are 40% – 85%). This change in the direction of cyclocondensation is, apparently, attributable to association of hydrazine or the hydrazino group with the heterofunctional group *via* hydrogen bonds (see also Section III.7.a).

c. Reductive heterocyclisation of 2,3-dialkynyl-1,4-naphthoquinones

The enediyne system, which is partially involved in the quinoid ring, imparts particular chemical specificity to 2,3-dialkynyl-1,4-naphthoquinones **160**. Upon treatment with hydrazine in dioxane at 50 – 60 °C, these compounds undergo unusual heterocyclisation to give 1,3-disubstituted 2*H*-*N*-aminobenzo[*f*]isoindole-4,9-diones **161**.[94, 102] Apparently, the initial step of this reaction consists in reduction of the enediyne system to the tetraene one. The resulting bis-allenylidene intermediate **162** adds NH_2NH_2 at the double bonds activated by the carbonyl groups and undergoes isomerisation. Therefore, hydrazine serves as both a reducing and heterocyclising agent.

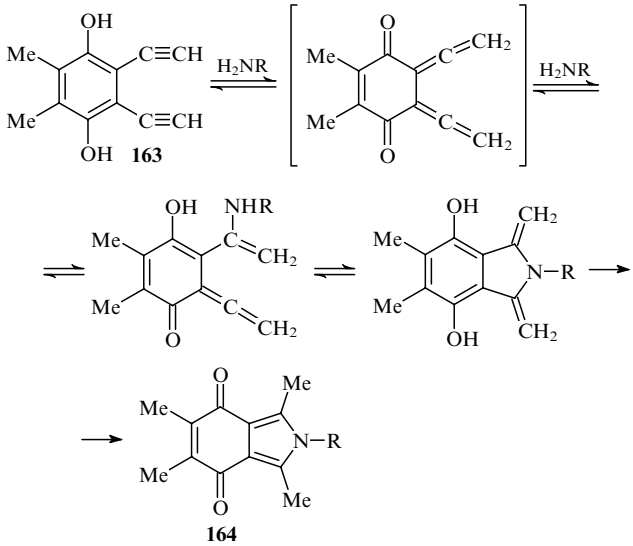


161 (53% – 80%)

R = $C(OH)Me_2$, , $C(OMe)Me_2$, Ph.

According to the results of X-ray diffraction analysis, 2*H*-benzo[*f*]isoindole-4,9-dione is a planar polycyclic system. The distinguishing feature of this compound is that the quinoid and pyrrole rings share the aromatic C – C bond, which has a lower bond order. This bond length in the 2-amino-1,3-dibenzyl derivative is 1.434 Å (the other C – C bond lengths in the pyrrole ring are 1.370 Å).

Interestingly, a short time before the discovery of this heterocyclisation, the reaction of 2,3-diethynyl-5,6-dimethylhydroquinone (**163**) with primary amines was described.[103] The latter reaction gives rise to 2-substituted 1,3,5,6,-tetramethylisoindole-4,7-diones **164** and proceeds, in essence, by an analogous mechanism.



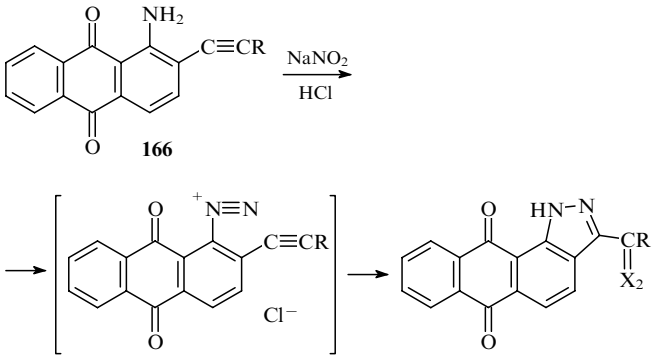
R = H, Me, Et, Pr, Bu, Ph.

A compound which bears the phenylethynyl substituents and is related to hydroquinone **163**, is not involved in analogous condensation with amines. Apparently, this may imply that cyclisation of bis-alkynyl-1,4-naphthoquinones does not afford bis-alkynylhydroquinones and the enediyne system of the substrate is reduced with hydrazine to the 1,2,4,5-tetraene system through another mechanism.

Taken together, these data provide a better insight into the essence of the chemical process responsible for both condensation reactions and give promise that a general procedure for the synthesis of this class of heterocyclic quinones will be developed.

8. Heterocyclisation of *vic*-acetylenic derivatives of anthraquinonediazonium salts

Intramolecular cyclisation of *ortho*-alkynylarenediazonium salts (Richter reaction) provides the basis for a general method for the synthesis of 4-hydroxy- and 4-halocinnolines.[104, 105] In attempting to extend this reaction to quinone derivatives, it was found that 2-alkynylanthraquinone-1-diazonium chlorides **165a**, which were prepared by diazotisation of the corresponding amines **166** ($NaNO_2$ in a mixture of dioxane and dilute HCl at 20 °C), underwent cyclisation to form the pyrazole rather than the pyridazine ring giving rise to 1*H*-3-(1,1-dichloroalkyl)- or 1*H*-3-acylnaphtho[2,3-*g*]indazole-6,11-diones of the general formula **167**.[24, 106, 107]



166 → **165a** → **167a**,**b** (62% – 83%)

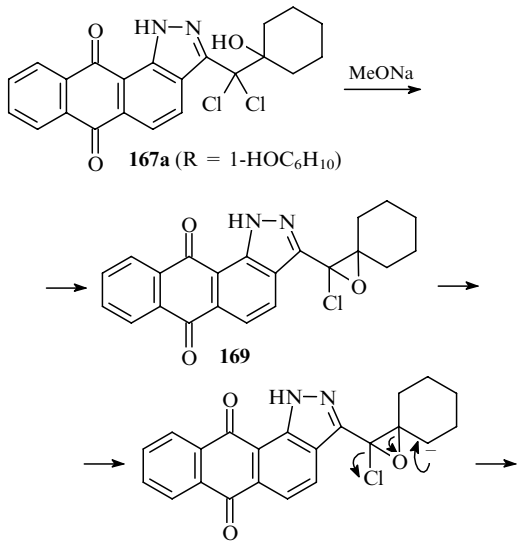
R = H, Bu, CH_2OPh, , COPr, $COBu^t$, COPh, Ph;

X_2 = O (**167a**), Cl_2 (**167b**).

If the triple bond in the acetylenic substituent of the starting compound is conjugated with the carbonyl or aryl group, the reaction affords acyl derivatives of naphthoindazoledione **167a**,[107] otherwise it gives α,α-dichloroalkyl derivatives **167b**.[24] Cyclisation of the former proceeds more slowly.

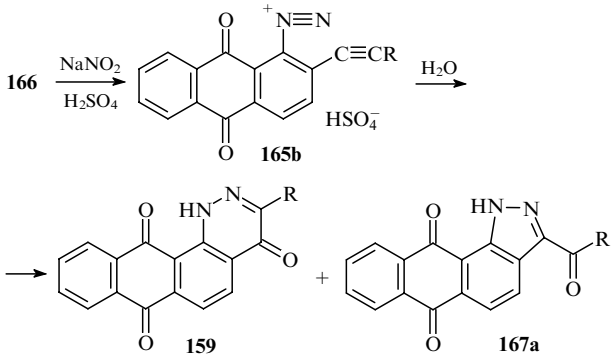
Dichlorides **167b** can be transformed into the corresponding ketones by treatment with MeONa in MeOH followed by acid hydrolysis of the resulting acetals.[24]

In reactions with MeONa, 1*H*-3-[(1-hydroxycyclohexyl)dichloromethyl]naphtho[2,3-*g*]indazole-6,11-dione (**167b**, R = 1-HOC_6H_{10}), unlike other dichlorides, is subjected to dehydrochlorination accompanied by migration of the oxygen atom to give cyclohexenyl ketone **168**.[107] Apparently, the reaction proceeds through the intermediate formation of epoxide **169**.



167a (R = 1-HOC_6H_{10}) → **169** → **168** (73%)

Cyclisation of diazo compounds **165b** was carried out under conditions which differ from those used for cyclisation of diazonium chlorides **165a**.[108] The steps of diazotisation of amines **166** and cyclisation of diazo compounds **165b** were separated. For this purpose, diazotisation of amines **166** was carried out in a mixture of acetone and dilute H_2SO_4 at 20 °C with the use of a 3 – 4 fold excess of $NaNO_2$, which made it possible to decrease the reaction time to 1 – 2 min. After completion of diazotisation, the solution of the diazonium salt was diluted with water or dilute H_2SO_4, thus providing the desired acidity of the medium in the step of cyclisation. The reaction was carried out at 65 °C. The exclusion of chloride anions from the reaction sphere changes its direction and the reaction affords naphthoindazolediones **167a** along with 1*H*-naphtho[2,3-*h*]cinnoline-4,7,12-triones **159**. The percentage of compounds **159** increases with increasing concentration of H_2SO_4 and they become virtually the only reaction products (yields are 71% – 91%) as the concentration of H_2SO_4 reaches 38%.



166 → **165b** → **159** + **167a**

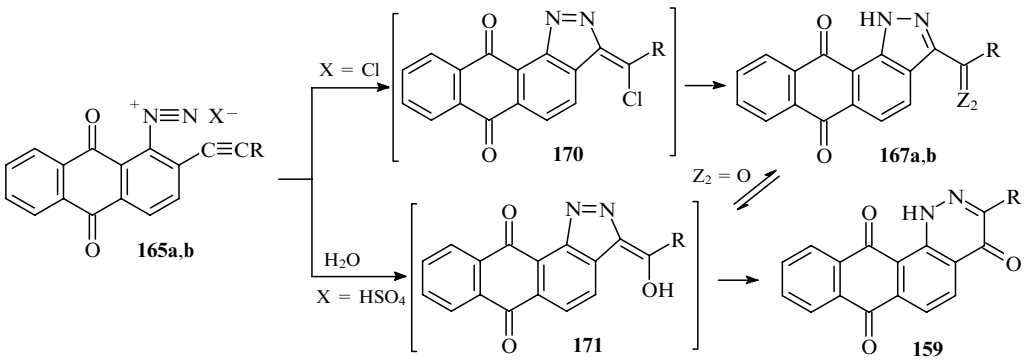
R = H, Bu, $CH(OH)Pr^n$, $CH(OH)Pr^i$, CMe_2OH.

The reason for the influence of the counterions (Cl^- or HSO_4^-) on the course of cyclisation of salts **165** can be understood taking into account the data obtained in the in-depth study of the cyclisation mechanism of acetylenic derivatives of 1,4-naphthoquinone diazonium salts (see below).[109] In the case of highly nucleophilic chloride ions, 1-chloroalkylidene derivative **170** is generated as the key intermediate, which gives product **167a** or **167b** containing the five-membered ring. In the case of non-nucleophilic bisulfate ions, the nucleophilic addition of water giving rise to intermediate enol **171** takes place. The latter can undergo tautomerisation to ketone **167a** or rearrangement to pyridazine derivative **159**. This rearrangement becomes the major process as the concentration of the acid increases (Scheme 5). Therefore, cyclisation of diazonium salts prepared from 2-alkynyl-1-aminoanthraquinones enables one to synthesise derivatives of either 1*H*-naphtho[2,3-*g*]indazole-6,11-dione **167** or 1*H*-naphtho[2,3-*h*]cinnoline-4,7,12-trione **159** depending on the reaction conditions.

Cyclisation of naphthoquinonediazonium chloride **172** was carried out analogously to cyclisation of compounds **165b**.[109] The starting amine was diazotised with an excess of $NaNO_2$ in a mixture of dilute HCl and acetone and diluted with water, 18% HCl or a NaCl solution. It was found that the reaction proceeds through the formation of pyrazole intermediate **173**, which is subsequently transformed with either ring expansion or retention of the size of the heterocycle to give the final reaction products **174** – **176**. The compositions of the products depend on the cyclisation conditions.

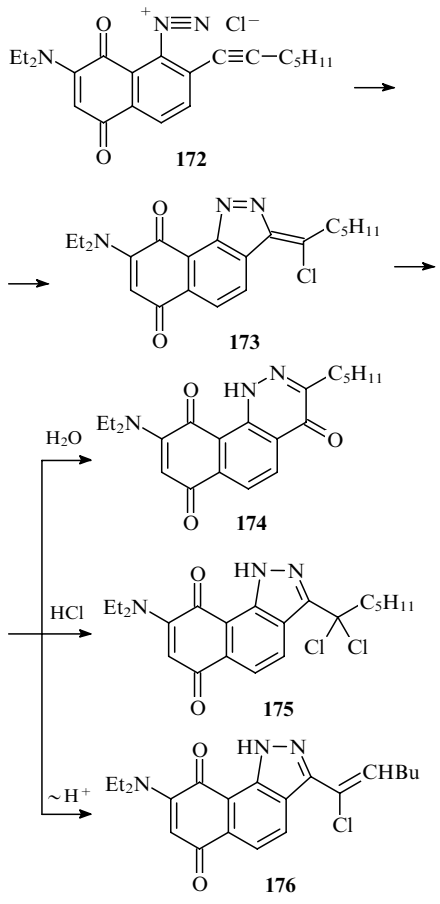
In hydrochloric acid medium, intermediate **173** is generated at a high rate and a large portion of the diazo salt is transformed into

Scheme 5



X = Cl (**a**), HSO_4 (**b**); Z_2 = O (**167a**), Cl_2 (**167b**).

this intermediate already within a few minutes. At that instant, the intermediate can be extracted from the reaction mixture with an organic solvent. Actually, it was isolated in this way in 79% yield. Intermediate **173** is chemically labile and can be transformed either with retention of the size of the heterocycle or its expansion not only in aqueous reaction systems but also on an adsorbent in an organic solvent. The mechanism of its transformation into the final products remains to be elucidated.

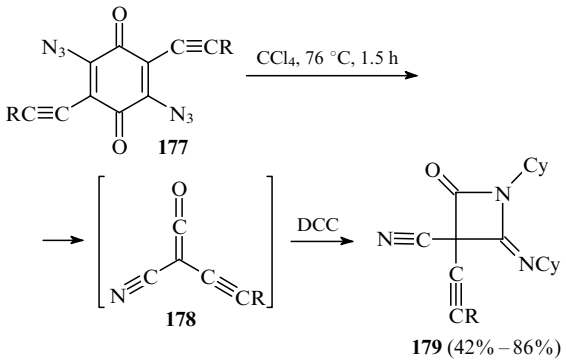


Reaction conditions	Yield (%)		
	174	**175**	**176**
H_2O, 20 °C, 5–6 h	80	–	–
HCl–$CHCl_3$, 7 h	25	60	16

Studies of cyclisation of alkynylquinonediazonium salts demonstrated that this process involves several steps. The reaction is, apparently, initiated by the attack of a nucleophile on the positively charged β-carbon atom of the acetylenic substituent resulting in the appearance of a negative charge on the α-carbon atom and a change in the geometry of this substituent. This leads to the closure of the heterocycle involving the α-C atom to give an intermediate of type **173**. It should be noted that the multistep mechanism of cyclisation of alkynylquinonediazonium salts is in contradiction with the mechanism of the Richter reaction represented as a concerted process of the direct formation of a six-membered heterocycle.[110]

9. Thermolysis of acetylenic derivatives of azidobenzoquinones

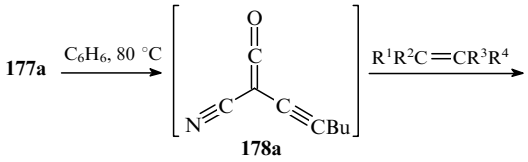
At temperatures above 75 °C, 3,6-dialkynyl-2,5-diazido-1,4-benzoquinones (**177**) are subjected to thermolysis to form alkynylcyanoketenes **178**.[111, 112] These compounds possessing the triple bond conjugated with the ketene group are unstable but can be fixed as rather stable adducts, for example, as azetidinones **179**, by performing the process in the presence of dicyclohexylcarbodiimide (DCC).[112]

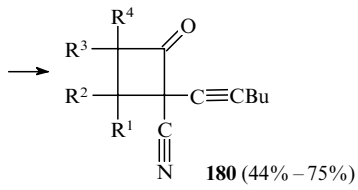


R = Bu (**a**), CMe=CH_2, CH_2OTHP, $(CH_2)_2Ph$, Ph, *o*-MeC_6H_4, *o*-$MeOC_6H_4$; Cy is cyclohexyl.

Schiff bases can also be used as trapping agents. For example, *N*-benzylideneaniline and *N*-(δ-phenylcinnamylidene)aniline react with ketene **178** to form β-lactams, whereas *N*-cinnamylideneaniline gives δ-lactams according to the [2+2]- and [2+4]-cycloaddition reactions, respectively.[111]

Alkynylcyanoketenes **178** are very reactive and, like most ketenes, are readily involved in cycloaddition to alkenes.[112] Hexynylcyanoketene **178a** reacts with substituted alkenes to form the corresponding substituted 2-(hex-1-ynyl)-2-cyanobutanones **180**. Cycloaddition of the ketene proceeds with retention of the configuration of alkenes.

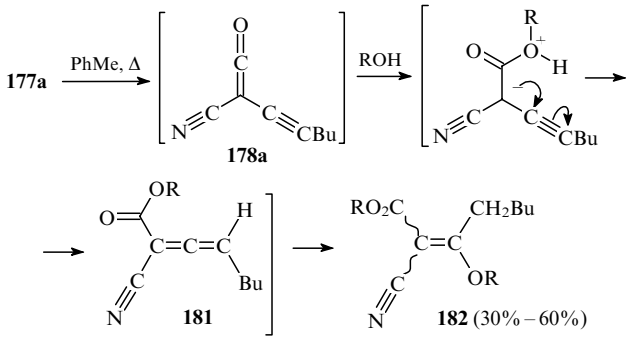




180 (44% – 75%)

$R^1 = R^3 = H$: $R^2 = R^4 = Et$, $R^2 – R^4 = –(CH_2)_4–$;
$R^1 = R^2 = R^3 = Me$: $R^4 = H$, Me.

The reactions of alkynylcyanoketenes **178** with alcohols are more complicated than those of simple ketenes.[111, 112] The initial nucleophilic attack of alcohol on the carbonyl group of ketene **178a** results in 1,4-addition to the enyne fragment to form 2-cyanoalka-2,3-dienoic acid ester (**181**). Then this allenic intermediate adds the second alcohol molecule to give 3-alkoxy-2-cyanoalk-2-enoic acid ester (**182**) as a mixture of *Z* and *E* isomers.

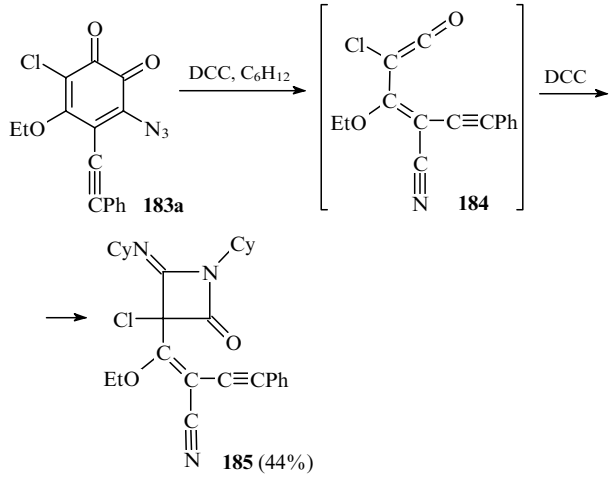


177a; **178a**; **181**; **182** (30% – 60%)

R = Pr^n, Pr^i, Bu^t, CH_2Ph.

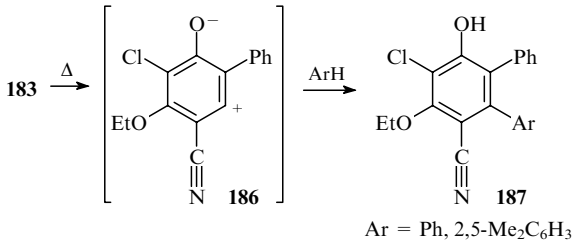
The reaction is carried out by gradually adding a solution of 3,6-dialkynyl-2,5-diazido-1,4-benzoquinone **177** in toluene to refluxing alcohol.

4-Acetylenic derivatives of 3-azido-6-chloro-5-ethoxy-*o*-benzoquinone are also subjected to thermolysis giving rise to ketenes. For instance, refluxing of compound **183a** in cyclohexane affords (2-cyano-1-ethoxy-4-phenylbut-1-en-3-ynyl)chloroketene (**184**), which is easily trapped with dicyclohexylcarbodiimide as the corresponding azetidinone **185**.[113, 114]



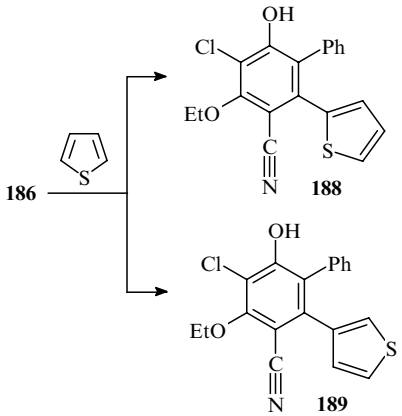
183a; **184**; **185** (44%)

Investigation of the reactions of ketenes generated from *o*-quinones **183** provided evidence that in the absence of trapping agents, these compounds undergo cyclisation to zwitterionic (or, probably, biradical) intermediate **186**, which is transformed into substituted phenol in reactions with external nucleophilic reagents or nucleophilic centres present in the molecule.[113] A solvent can also serve as a nucleophile when decomposition of the starting quinone is carried out by refluxing in benzene, *para*-xylene or thiophene.[113, 114] For example, products **187** – **191** are generated from azidoquinone **183a**.

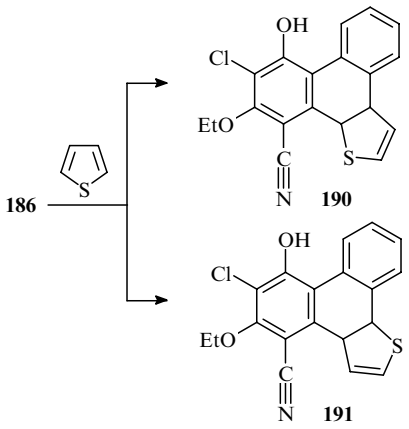


183; **186**; **187**

Ar = Ph, 2,5-$Me_2C_6H_3$

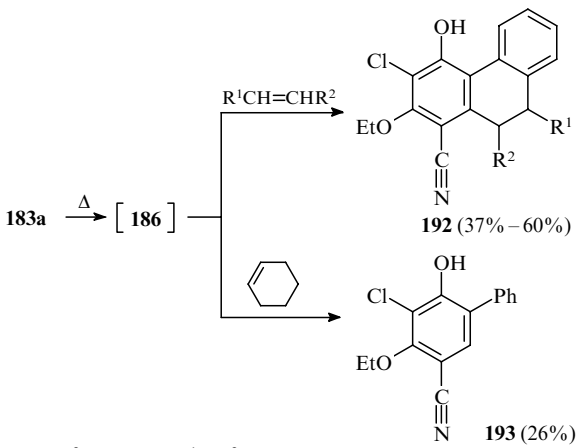


186; **188**; **189**



186; **190**; **191**

Thermolysis of compound **183a** in the presence of alkenes, in which the double bond is conjugated with the π electrons of the aromatic ring or the lone electron pair of the heteroatom, affords substituted dihydrophenanthrenes **192** (analogously to the reaction with thiophene, which gives rise to product **191**).

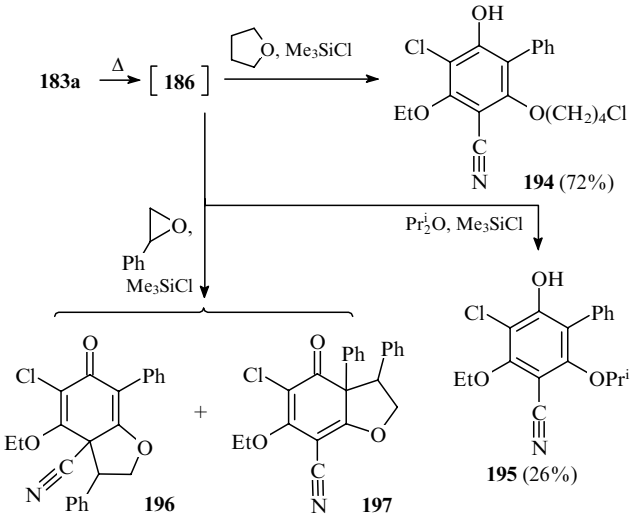


183a; **186**; **192** (37% – 60%); **193** (26%)

R^1 = Ph: R^2 = H, Ph; $R^1 – R^2 = –(CH_2)_3O–$.

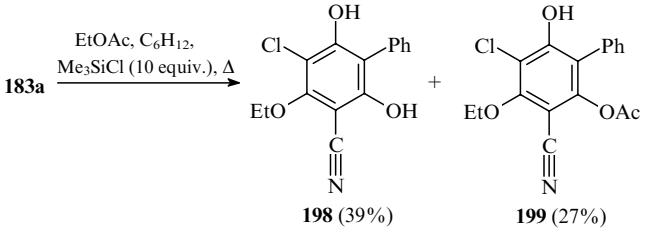
Under these conditions, such alkenes as cyclohexene or tetramethylethylene do not form adducts of type **192** with quinone, but they can serve as hydrogen donors. For instance, thermolysis of phenylethynylquinone **183a** in the presence of cyclohexene afforded a complex mixture of compounds, from which only 2-chloro-4-cyano-3-ethoxy-6-phenylphenol (**193**) was isolated.[114]

Cyclic and acyclic ethers react with zwitterionic intermediate **186** in the presence of Me_3SiCl.[114]

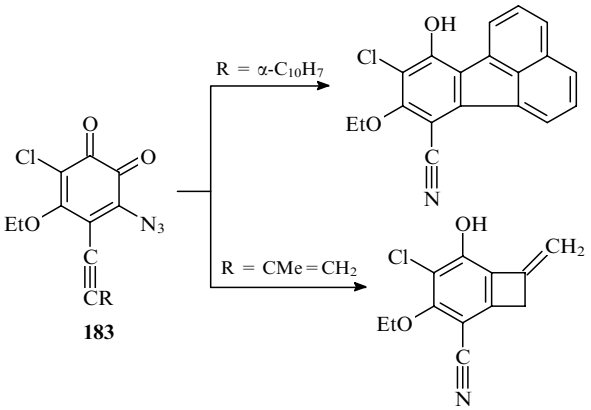


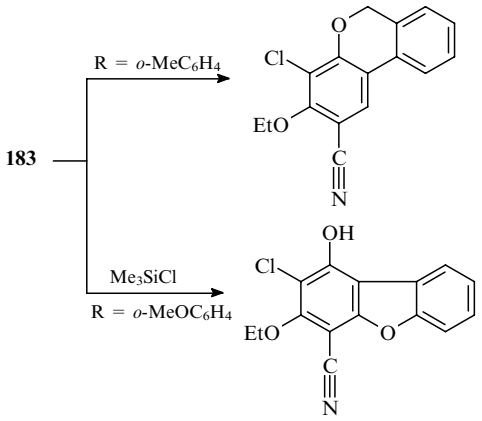
The reactions with tetrahydrofuran and diisopropyl ether give rise to alkoxy-substituted cyanophenols **194** and **195**. Under these conditions, styrene oxide produces two isomeric cyclohexadienones **196** and **197** in a ratio of ~1 : 1 in a total yield of 22%.

Thermal decomposition of compound **183a** in a mixture of ethyl acetate and cyclohexane in the presence of Me_3SiCl involves hydroxylation and partial acetoxylation of the zwitterionic intermediate to give resorcinol derivatives **198** and **199**.

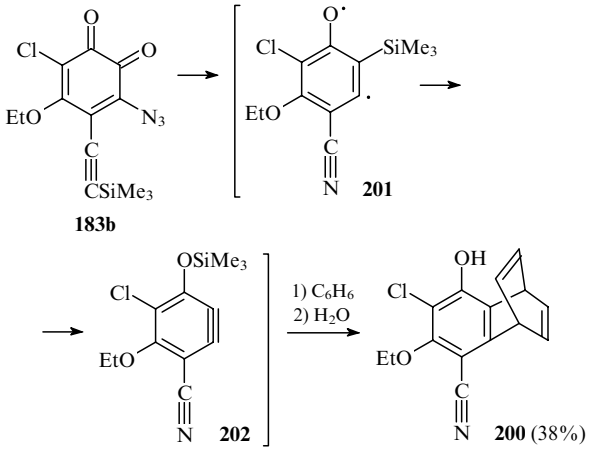


Intermediates generated upon thermolysis of other *ortho*-benzoquinones **183** can be stabilised intramolecularly with the involvement of a group of the acetylenic substituent to form polycyclic compounds (in 16% – 76% yields), which are difficult to prepare by other methods. In some cases, it is necessary to perform decomposition of the quinone in the presence of Me_3SiCl.





Thermal decomposition of the trimethylsilyl derivative of azido(ethynyl)-*o*-benzoquinone **183b** in benzene affords 2-chloro-4-cyano-5,8-etheno-3-ethoxy-5,8-dihydro-1-hydroxynaphthalene (**200**).[46] The authors believed that the reaction proceeds through biradical intermediate **201**, which is rearranged to substituted dehydrobenzene **202** through migration of $SiMe_3$ to the oxygen atom, and then compound **202** adds to benzene at positions 1,4.



10. Other reactions

Alkynylquinones are involved in the addition reactions at the triple bond (for example, such as hydration or hydrogenation) which are typical of acetylenes of various classes. It was found that 1- and 2-acetylenic derivatives of anthraquinone add water in concentrated H_2SO_4 on heating to 40 – 80 °C for 1 – 5 min or in dioxane in the presence of catalytic amounts of $HgSO_4$ and dilute H_2SO_4 (80 °C). Ethynyl and phenylethynyl derivatives give the corresponding acetylquinones and phenacylquinones, respectively.[18, 19, 29, 30] Hydrogenation of the triple bond to the double bond in alkynylquinones on a deactivated palladium catalyst is generally accompanied by reduction of the carbonyl groups to give hydroquinones, which are readily oxidised with aqueous $FeCl_3$ or atmospheric oxygen in the course of isolation.[6, 31]

Ethynyl derivatives of quinones are also involved in usual reactions proceeding with the replacement of terminal hydrogen. Thus, *vic*-amino(ethynyl)anthraquinones are easily acylated by carboxylic acid chlorides in the presence of Et_3N and $Pd(PPh_3)_2Cl_2$ or the same palladium complex in combination with CuI in benzene. This method procedure was used for the synthesis of benzoylethynyl- and pivaloylethynylanthraquinones in 67% – 95% yields from 1-amino-2-ethynyl-, 1-amino-3-chloro-2-ethynyl- and 2-amino-3-ethynylanthraquinones.[36, 58, 78, 79] Cadiot – Chodkiewicz coupling of 3-diethylamino-5-ethynyl-1,4-naphthoquinone with 1-bromo-3-methylbut-1-yn-3-ol and Mannich aminomethylation of the former provide examples of the Cu-

catalysed replacement of the hydrogen atom of the ethynyl group in the quinone series.[69]

The alkaline cleavage of tertiary acetylenic alcohols (retro-Favorskii reaction), which is used for the synthesis of ethynyl-, diethynyl- and butadiynylquinones, belongs to a class of cleavage reactions in which the triple bond remains intact.[13, 14, 37, 69] Decomposition of alcohols is generally carried out in the presence of KOH (sometimes with an addition of dibenzo-18-crown-6 or a mixture of CaO and Na_2SO_4) in benzene or toluene at 60 – 110 °C (yields are 20% – 89%).

$$\text{Quin}[(C{\equiv}C)_nCMe_2OH]_m \xrightarrow{KOH} \text{Quin}[(C{\equiv}C)_nH]_m$$

For the preparation of compounds containing the ethynyl group in the quinoid ring, this method is, apparently, applicable only in exceptional cases.[69]

IV. Conclusion

Acetylenic derivatives of quinones belong to a new group of polyfunctional compounds containing the activated triple bond. Their chemical properties are determined also by the presence of a mono- or polycyclic quinoid moiety containing a specific labile π-electron system and several reaction centres. Each reaction centre possesses particular inherent physicochemical properties, which influence each other and change the properties of the molecule as a whole. For instance, the triple bond in alkynylquinones possesses high electrophilicity due to the influence of the electron-withdrawing quinoid moiety regardless of the position of the acetylenic substituent, and this fact has a substantial effect on the reactivity of these compounds. For example, the nucleophilic addition of hydrazine at the triple bond of 1-alkynylanthraquinones, which proceeds readily and regiospecifically, leads to the closure of the sterically hindered diazepine ring involving the carbonyl group in the *peri* position. Under the reaction conditions, this ring can unexpectedly be transformed into the pyridine ring with a 'loss' of the nitrogen atom (see Section III.7.a). The ability to add N-nucleophiles in the absence of a catalyst also provides the basis for an original procedure for the closure of the pyrrole ring in *vic*-amino(alkynyl)anthraquinones (see Section III.2.b). Reductive cyclocondensation of 2,3-bis-alkynyl-1,4-naphthoquinones with NH_2NH_2 is used for the synthesis of isoindolequinones (see Section III.7.c), which are difficult to prepare by other methods. This reaction is *a priori* unpredictable and is, apparently, typical only of compounds containing two vicinal acetylenic substituents in the quinoid ring. Of other specific reactions of alkynylquinones, let us mention the non-trivial thermal cleavage of azidobenzoquinone derivatives, which serve as precursors of very reactive highly unsaturated ketenes (see Section III.9).

These and the above-considered data on the chemistry of acetylenic derivatives of quinones show that these compounds possess a high synthetic potential. It is evident that these compounds hold promise as key intermediates in the synthesis of fused heterocyclic quinoid structures with the aim of searching for new pharmaceuticals and industrial materials. These compounds are, apparently, applicable also for preparing immobilised biologically active quinones, film sensitisers, immobilised redox systems, components of liquid-crystalline composites, *etc*. However, some aspects of the chemistry of alkynylquinones remain unknown. Data on transformations of alkynyl-*ortho*-quinones and quinones containing acetylenic substituents in the quinoid ring are scarce. Efficient general methods for the synthesis of such compounds remain to be developed. The biological activities of alkynylquinones have been poorly studied.

This review will hopefully be found interesting and useful by chemists and contribute to the progress in the chemistry of acetylenic derivatives of quinones, their use in the practice of fine organic chemistry and pharmacological investigations.

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