

SIMPLE AND EFFECTIVE APPROACHES TO COUMESTANS AND AZACOUMESTANS

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Abstract - Coumestans and its mono- and diaza-analogs (**1-4**), which possess potential estrogenic or antiestrogenic activities, can be synthesized easily in excellent yields (60-95%) by the following four methods, starting either from 4-hydroxy-3-arylcoumarins and -quinolones (**16**) (or from 4-amino derivatives (**19**)) by catalytic dehydrogenation or reacting 3-hydroxy-3-arylquinoline-2,4-diones (**21**) by acid-catalyzed dehydration. Phenyl ethers (**25**) cyclize by catalytic or photochemical dehydrohalogenation to give **1** or **2**. Another way is the thermal or photochemical decomposition of 4-azido-3-aryl derivatives (**28**) to the azacoumestans (**3-4**).

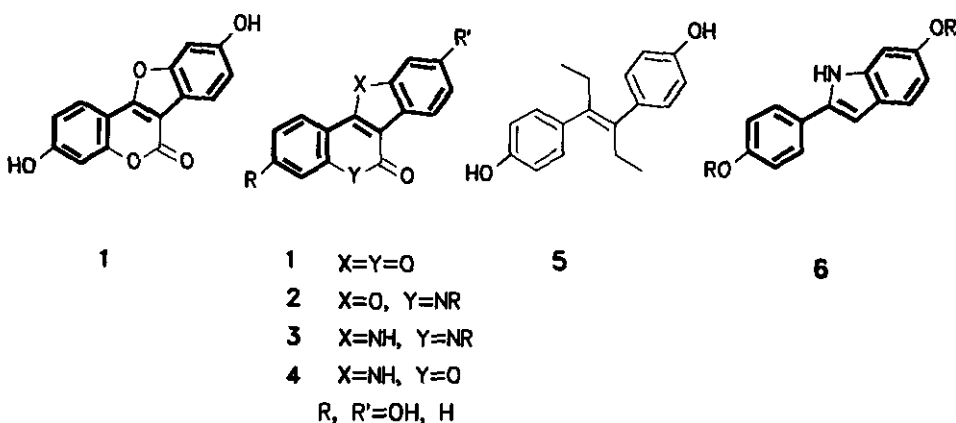
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* Dedicated to Professor E. C. Taylor with best wishes on the occasion of his 70th birthday.

1. Introduction

The basic ring system of a number of natural products includes the coumestan ring system (6*H*-benzofuro[3,2-*c*]benzopyran-6-one), which is found *e.g.* in coumestrol, psoralidine or pterocarpin.¹ Coumestrol, the dihydroxy derivative (**1**), represents an estrogenic factor² occurring naturally in forage crops.

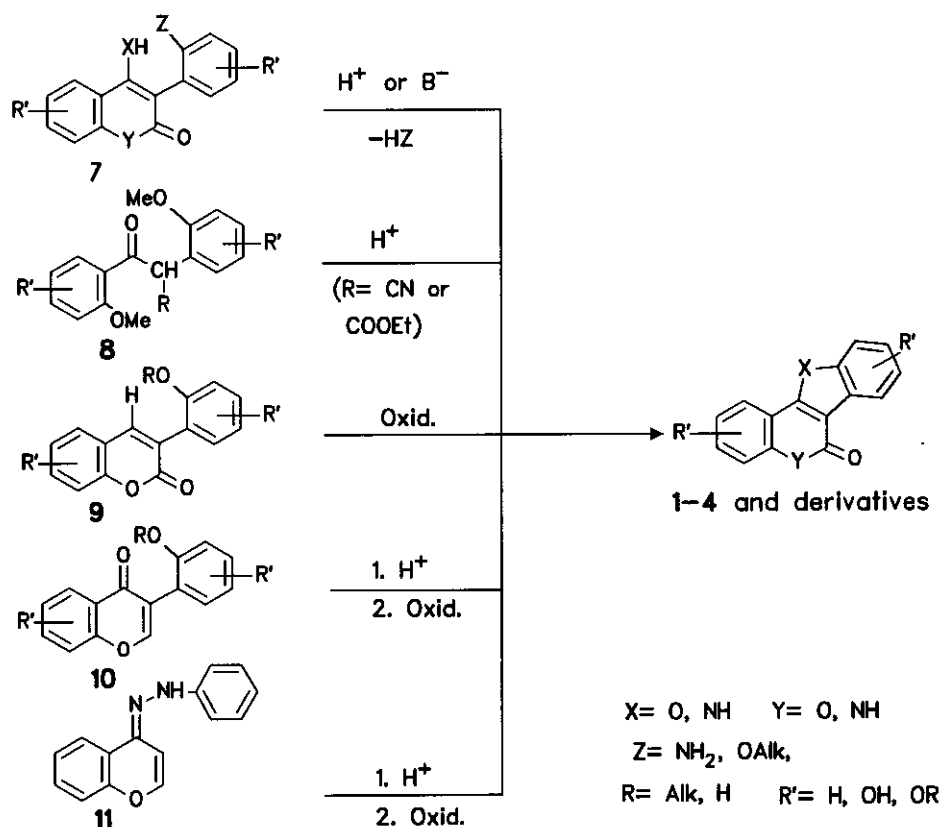


It is easily noted that the 4,4'-dihydroxy-*E*-stilbene moiety (bold faced) as in diethylstilbestrol (**5**), is present in this structure, as well as in the corresponding 2-phenylindole system (**6**). The estrogen receptors, a specific high-affinity binding protein present in estrogen-sensitive tissues, is the principal mediator of estrogen activity. Also human breast tumor cells are known to have significant levels of estrogen receptor.³ Some synthetic estrogens, such as stilbestrol and hexestrol, show a similar binding activity as the natural hormone.⁴ Therefore some non-steroidal estrogen antagonists based on (*E*)-4,4'-dihydroxystilbene (*e.g.* **5**) have already been successfully introduced⁵ in the treatment of advanced breast cancer or are in development.⁶ Similar results could be obtained with 2-phenylindole systems (**6**)⁷ and 2,3-diarylbenzopyranes.⁸ Moreover, recently azacoumestans of type (**2**) were found possessing an antiosteoporotic activity.⁹

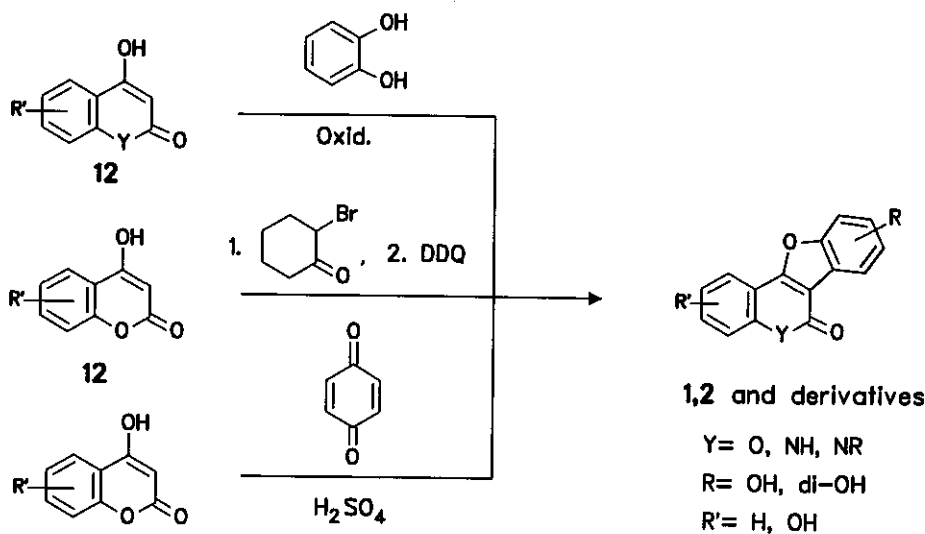
Fused ring systems, which contain both the indole and the quinoline nucleus, represent another type of natural products, the carboline ring system. Diazacoumestans correspond to the alkaloids of the 3,4-benzo- γ -carboline type, which are found *e.g.* in ibogamine¹⁰ or are have pharmacological activity.¹¹

2. A literature survey for synthetic pathways to coumestans and azacoumestans

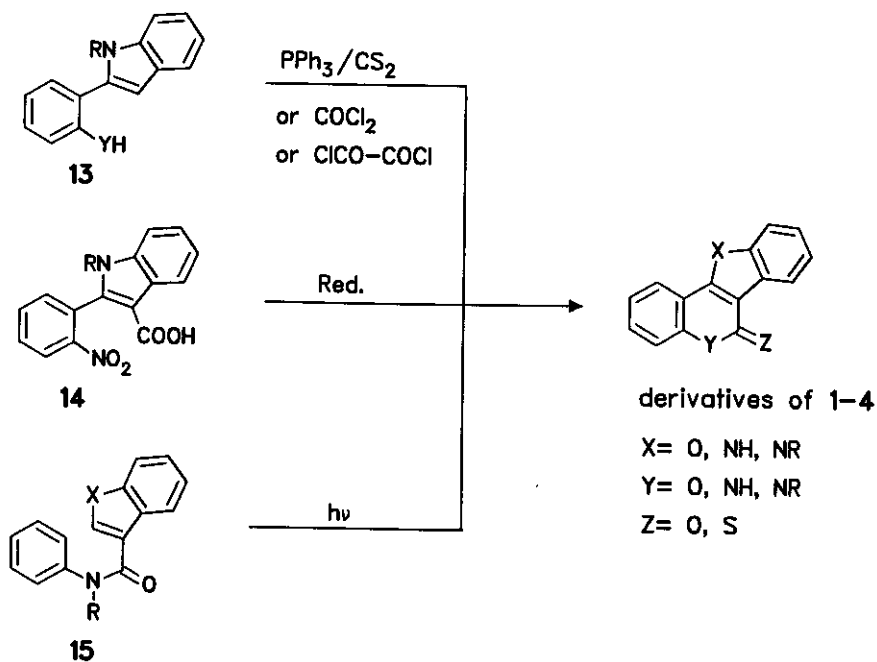
Synthetic methods found in the literature to afford coumestan and azacoumestan ring systems consist mainly of three kinds of cyclization reactions. One type is the formation of a single bond by the ring closure of 4-hydroxy- or 4-aminocoumarins and -quinolines (or precursors of these heterocycles) either with a 3-aryl substituent having a reactive *ortho* substituent such as hydroxy (**7**), (**9**), (**10**)¹³, alkoxy (**7**), (**8**)^{9, 12, 14, 15} or fluoro (**7**)¹⁶ or by Fischer-indole cyclization of a phenylhydrazonochromene (**11**).¹⁷



A second type includes the connection of two bonds by oxidative condensation of 4-hydroxy-coumarins (**12**) with 1,2-benzendiols,¹⁸ quinones¹⁹ and related compounds.²⁰ Oxidation was performed either with inorganic oxidation agents (e.g. periodates), also electrochemical or enzymatic methods were used.



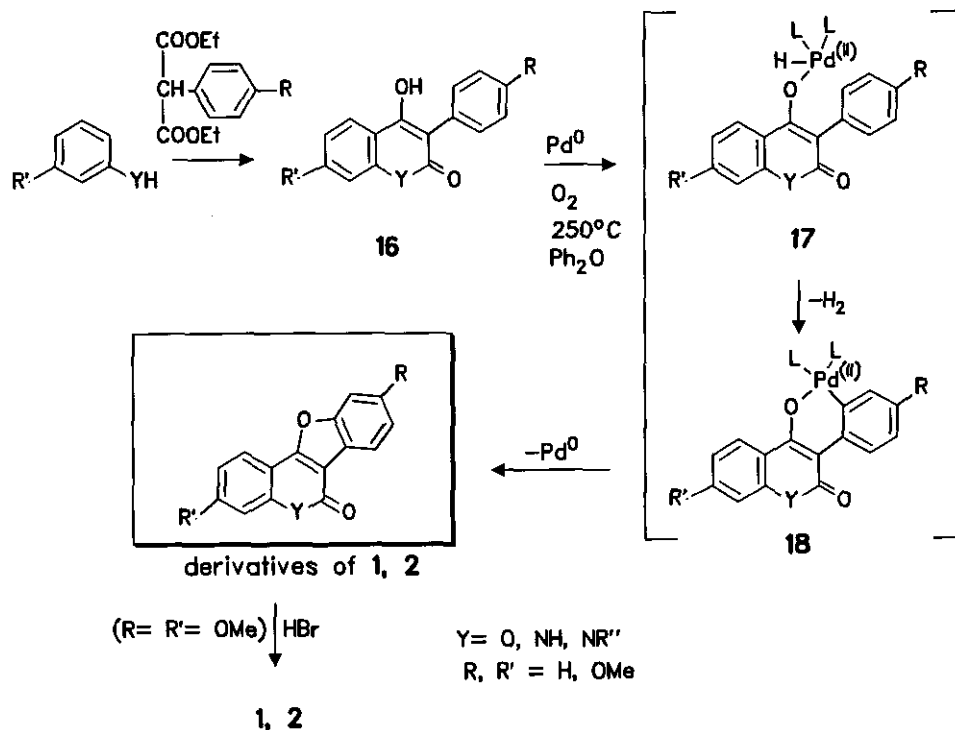
A further reaction sequence starts from benzofurans or indoles. So cyclization of 2-arylindoles (**13**) having an amino or hydroxy substituent in *ortho* position of the aryl ring can be cyclized using a C-1 building element.²¹ A similar ring closure was reported using the corresponding 2-arylindol-3-carboxylates (**14**).²² Connection of a bond in indole-3-carboxanilides (**15**)²³ could be shown to yield again coumestrols and azacoumestrol (**1-4**).



Some of the reactions to coumestans and azacoumestans reported in the literature need a multi step synthesis by using starting materials, which are often not easy available. Other syntheses result in substitution patterns or isomers which are not desired. So we have developed a number of synthetic entries to coumestrols (**1**), azacoumestrols (**2**) or (**4**) and diazacoumestrols (**3**), which will be described.

3. Palladium catalyzed cyclodehydrogenation of 3-arylcoumarins and 3-aryl-2-quinolines having a 4-amino or 4-hydroxy group.

Our affair with coumestrols developed many years ago during the study of dehydrogenation reactions with a palladium catalyst. In a special case which involved the reaction of a tricyclic 4-hydroxy-3-phenyl-2-quinolone of type (**16**), we observed also a cyclodehydrogenation between the hydroxy group and the phenyl ring leading to a condensed benzofuran system (**2**) with an azacoumestrol frame.²⁴ The value of this reaction for the synthesis of the coumestan system was readily recognized, and the reaction was extended to the synthesis of coumestrol (**1**) and other benzofuran systems.²⁵



Although the required temperature of 250°C for this reaction is rather high, this method has later been used effectively by others for the synthesis of rather complex coumestans (Brya-carpenon-3).²⁶ A systematic study²⁷ of the reaction parameters (temperature, use of Pd(0) or Pd(OAc)₂ and co-catalysts, use of supplementary oxygen) in the cyclodehydrogenation reaction has shown that a uniform dehydrogenation reaction with palladium on charcoal can be observed at high temperatures (best results were observed at 250°C in boiling diphenyl ether). When the temperature was decreased to 140°C (boiling xylene), not only the yield decreased drastically (from 60-70% to 10-20%), but also a number of byproducts are formed, mainly 3-hydroxy-3-arylquinolinediones (**21**). It could be shown that bubbling air through the boiling solution brought better yields at 250°C, whereas at 140°C no improvement could be observed.

The initial step in the cyclization reaction is assumed to be an oxidative addition of Pd(0) to the enolized hydroxy group of the 1,3-dicarbonyl system of **16** forming the palladium complex (**17**) (probably with diphenyl ether as the ligands) in analogy to similar reactions²⁸ followed by an *ortho*-metallation step of the neighbouring phenyl ring to yield **18**. This six-membered palladium heterocycle (**18**) could react to the benzofuran (**1**, **2**) by the reductive palladium elimination step, which explains the strong dependence on the temperature.

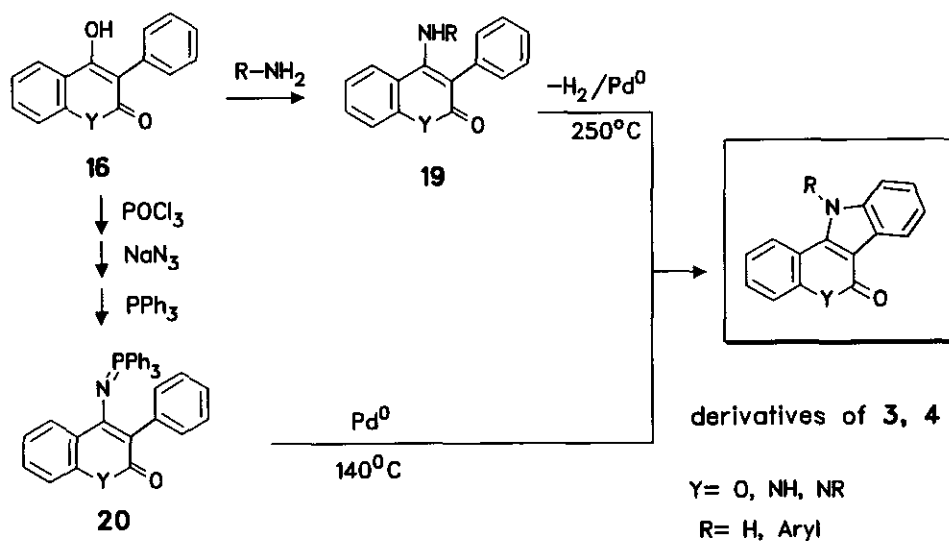
This considerations prompted us to experiment with Pd(II)-salts, which would not need the initial oxidation step. Actually, in this case the ring closure takes place in about 50% at temperatures of 60-80°C. By using the cooperation of oxygen the benzofurans (**1**, **2**) are obtained in purer form, but the yields do not increase. Raising the temperature to 140°C decreases both yield and purity. So in all aspects the cyclodehydrogenation with Pd(0) at 250°C in boiling diphenyl ether in the presence of oxygen affords the best results.

4-Hydroxy-3-arylcoumarins and -quinolones (**16**), which were used as starting compounds, are readily available from commercial starting materials, *e.g.* phenyl malonate and appropriate substituted phenols and anilines.²⁹ If substituents in the 3-phenyl ring are desired, the appropriate arylmalonates can be prepared *via* an oxalic ester condensation and decarbonylation of commercially available arylacetic acids or esters.³⁰ Recently, a new method for direct arylation

of 4-hydroxycoumarins was introduced using aryllead triacetates or triaryl)bismuth diacetates,³¹ which avoids the synthesis of arylmalonates.

Whereas coumestrol dimethyl ether (**1**, Y= O, R= R'= OCH₃) could be obtained by cyclodehydrogenation in 25% yield,²⁵ the corresponding dimethoxyazacoumestrols (**2**, Y=NH or NR, R= R'= OMe) only could be obtained in very low yields and as impure products.²⁷

4-Amino-3-phenylcoumarins and -2-quinolones (**19**), which were obtained from the corresponding 4-hydroxy compounds (**16**), can be cyclized to the aza- and diazacoumestans (**3**) and (**4**) by cyclodehydrogenation by using the same conditions as described above (boiling diphenyl ether, Pd(0) on charcoal, regeneration of the catalyst by bubbling air through the reaction mixture).³²



With anilincoumarins and -quinolones (**19**, R= Ph), the azacoumestans (**3**) and (**4**) were obtained in 90% yields. With 4-amino compounds (**19**, R= H), however, the yields decreased significantly to 13 and 30%. Attempts to improve the yields by acetylating the amino group was not successful: the yields increased only from 15 to 17%.

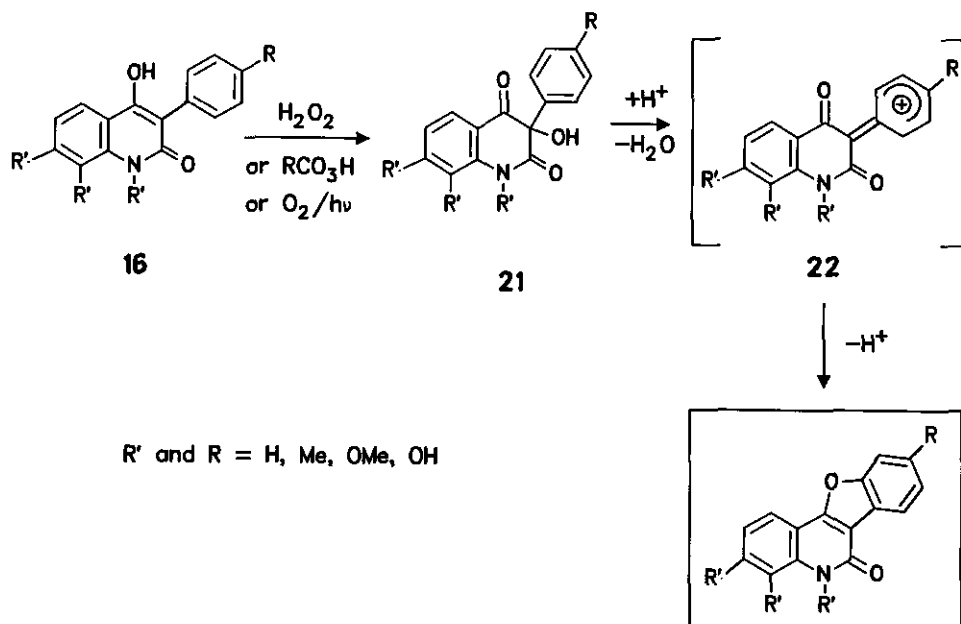
Alkylaminocoumarins and -quinolones (**19**, R= alkyl) did not cyclize to indoles (**3**, **4**). Either the alkyl group was cleaved to yield impure *N*-unsubstituted azacoumestans (**3**, **4**), or, in the case

of benzyl substituted (**19**) ($R = \text{CH}_2\text{C}_6\text{H}_5$) ring closure to an quinoline-condensed compound was observed.³²

The cyclodehydrogenation of the iminophosphoranes (**20**) can be performed at significantly lower temperatures. At 140°C in boiling xylene with $\text{Pd}(0)$ as catalyst, the ring closure takes place to yield diazacoumestans (**4**) ($Y = \text{NH}, \text{NR}$) in 25% yields,⁴⁴ but difficult purification destroys any advantages of this reaction.

4. Dehydration of 3-aryl-3-hydroxy-2,4-dioxotetrahydroquinolines

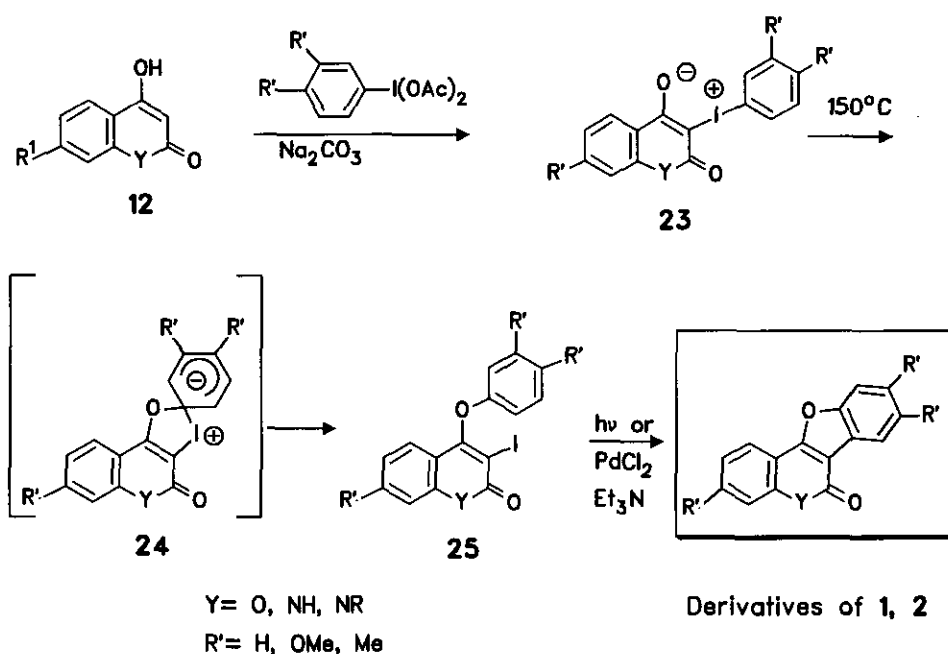
The starting materials, 3-aryl-3-hydroxy-2,4-dioxotetrahydroquinolines (**21**) are readily available by oxidation of 3-aryl-4-hydroxy-2-quinolones (**16**) with hydrogen peroxide in alkaline solution, peroxy acids such as 3-chloroperoxybenzoic acid or peracetic acid, by irradiation with uv light of 254 nm in the presence of oxygen³³ or by the addition of phenols to quinisatin (2,3,4-trioxo-tetrahydroquinoline).³⁴



Dehydration can be performed with strong acids such as sulfuric acid, methanesulfonic acid - phosphorus pentoxide or perchloric acid at elevated temperatures. Whereas sulfuric acid can only be applied with no or electron withdrawing substituents R and R' , otherwise also sulfonation takes place, the latter two acids, however, achieve good results. The reaction is supposed to proceed *via* the phenonium ion intermediate (**22**). The yields of the azacoumestans (**2**) are usually good, however, if $R = OH$ or CH_3O , the yield drops to 5% only.^{27,35} Furthermore, the reaction sequence works only in the quinoline series, since the corresponding benzo-pyran derivatives of **21** are not accessible.

5. Synthesis *via* iodonium-ylides - cyclodedyrohalogenation of coumarin- and quinolone-4-aryl ethers

The preparation of iodonium ylides (**23**) starting with 4-hydroxy-coumarins and 2-quinolones (**12**) unsubstituted at the 3-position is very simple and has been studied by us in another connection many years ago.^{36,37} Thus, **12** is treated with the required iodosylbenzenes prepared *in situ* from the corresponding diacetoxyiodoarenes with aqueous sodium carbonate to yield the iodonium ylides (**23**).^{36,38}



The rearrangement of **23** to the 4-aryloxy-3-iodo ring systems (**25**) occurs at about 150°C in aprotic polar solvents, and it is assumed to proceed as a variation of the Smiles rearrangement via a *spiro*-Meisenheimer complex (**24**)³⁷ (e.g. a *para* substituent on the phenyl ring in **23** is still in the *para* position after the rearrangement to **25**).^{27,36,38}

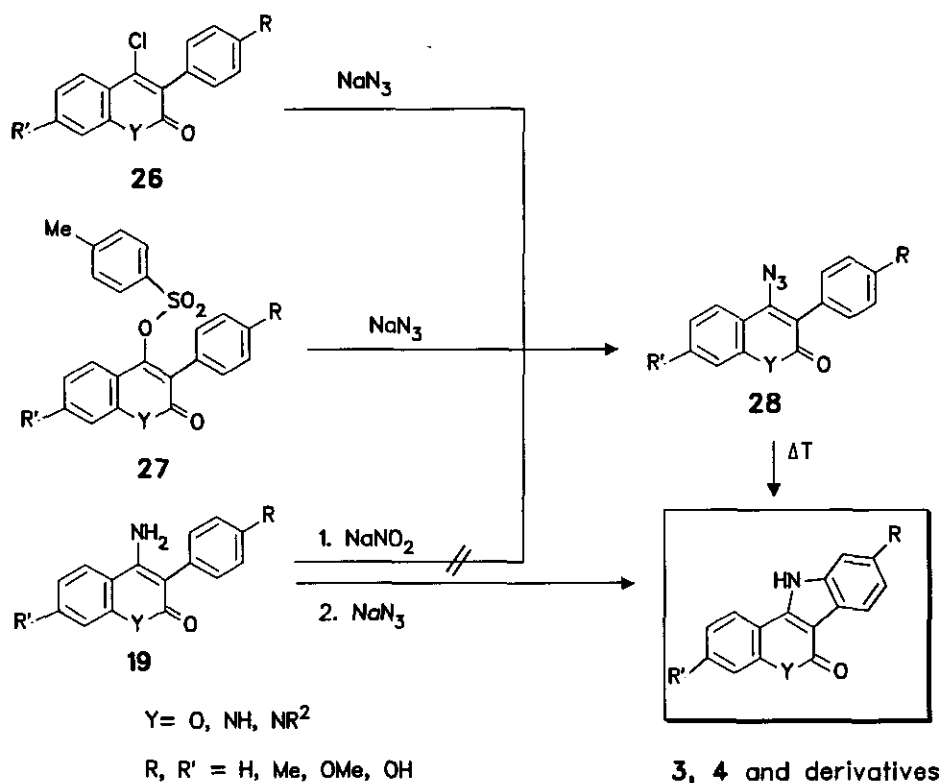
The photocyclization of the 3-iodo derivatives (**25**) (R' = H; Y = O, NH, NR) yields the coumestan or azacoumestan ring system of **1** or **2** in about 40%. Coumestan could also be obtained by photocyclization of 4-phenyloxycoumarin in the presence of iodine. With hydroxy or methoxyl groups at the phenyl ring, no photocyclization was possible.³⁸

These negative results prompted us to study the Ullmann³⁹ and Heck reaction⁴⁰ with 4-aryloxy-3-iodocoumarins and -quinolones. While the Ullmann reaction with copper and copper salts failed, the Heck reaction turned out to be a good choice. Among many tested conditions, the use of palladium chloride in triethylamine (which is used as a ligand and as trap for acids) gave the best results.^{27,41} Whereas in the rearrangement step **23** → **25** the methoxy substituted compounds were very sensitive against higher temperatures and showed lower yields than compounds with R' = H, the cyclization step **25** → **1,2** brought better yields in some cases than with the unsubstituted representatives.

6. Degradation of azides to azacoumestrols with an indole system

From our studies, we excluded cyclodehydrogenation reactions of 4-amino- or 4-triphenylphosphoranylideneaminocoumarins or -quinolones with methoxyl groups in the phenyl ring (R = OCH₃), because low yields of the desired azacoumestan ring systems of **3** and **4**^{32,44} were obtained already with no substituent (R = H) in the phenyl ring.

Ring closure reactions of 2-phenylvinylazides are known to give the corresponding indole derivatives.⁴² Azacoumestan ring systems (**3**) and (**4**), which contain also the biologically interesting 2-phenylindole moiety,⁷ could easily be obtained by thermal or photochemical degradation of 4-azido-3-arylcoumarins or -quinolones (**28**).⁴³

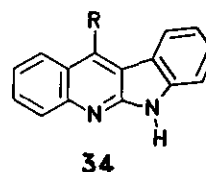
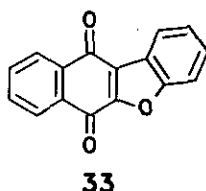
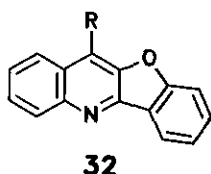
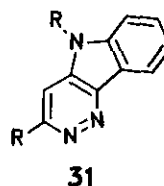
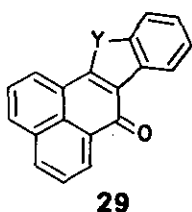


The azides (**28**) can be obtained either with sodium azide from the corresponding 4-chloro- or 4-tosyloxy compounds (**26**) or (**27**), respectively, which in turn could be obtained from the 4-hydroxy compounds (**16**) by chlorination with phosphoryl chloride or tosylation with tosyl chloride.⁴⁴ Another approach starts from 4-aminocoumarins and -quinolones (**19**), which cyclize after diazotation and azidation⁴⁴ directly by acid-catalyzed formation of a nitrenium ion (for nitrenium ions and mechanistic aspects see reference 45).

Application of suitable substituted azides (**28**) ($\text{R}=\text{R}'=\text{OCH}_3$) leads to the azacoumestrol derivatives (**3**) and (**4**), which can be converted into the receptor active azacoumestrols ($\text{R}=\text{R}'=\text{OH}$) by cleavage of the azacoumestrol ethers ($\text{R}=\text{R}'=\text{OCH}_3$) with hydrobromic acid.⁴⁶ In the quinolone series, we were not able to isolate the azide (**28**) ($\text{Y}=\text{NH}, \text{NR}$), because this azide could not be obtained at temperatures below 80°C . Higher temperatures caused a slow reaction to the azide but followed by a fast decomposition and indole cyclization to yield the diaza-coumestrols (**4**).⁴⁶

7. Other benzofuran and indolesystems obtained by cyclodehydrogenation, cyclodehydration and azide cyclization

Our methods could be applied to obtain some other similar benzofuran and indole systems, which are related to coumestan- and azacoumestan ring systems, as well as the ring systems present in other natural products.



2-Phenyl-3-hydroxy-1-phenalenones could be cyclized to afford benzofuran and indole ring systems of type (29),^{25,47} 5-arylbarbituric acids underwent ring closure to benzofurans and indoles of type (30),⁴⁸ both by cyclodehydrogenation, cyclodehydration and decomposition of azides. 4-Azido-3-phenylpyridazines cyclized to the indoles of type (31),⁴⁹ 3-hydroxy-2-phenylquinolines could be cyclodehydrogenated to form the benzofurans (32).²⁵ The natural product, *β*-brazanquinone (33), was obtained from 3-hydroxy-2-phenyl-1,4-naphthoquinone by cyclodehydrogenation.⁵⁰ Linear annellated indoloquinolines (*benzo-α-carbolines*) (34) were derived from 2-azido-3-phenylquinolines.^{43,51}

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Received, 30th November, 1992