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**).

CONTENTS

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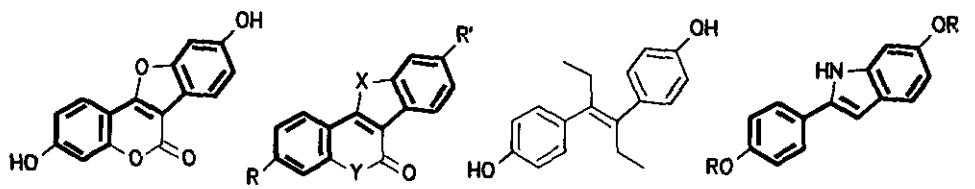
* Dedicated to Professor E. C. Taylor with best wishes on the occasion of his 70th birthday.

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 factor[2] occurring naturally in forage crops.



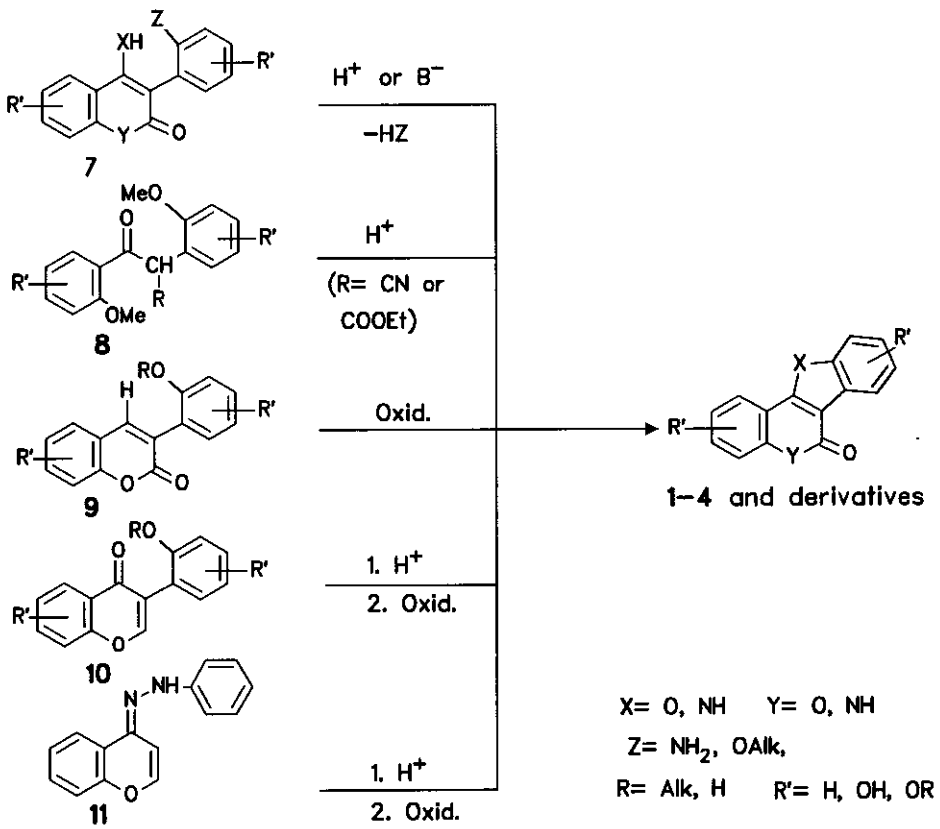
1 **1** X=Y=O **5** **6**
2 X=O, Y=NR
3 X=NH, Y=NR
4 X=NH, Y=O
R, R'=OH, H

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 introduced[5] 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]

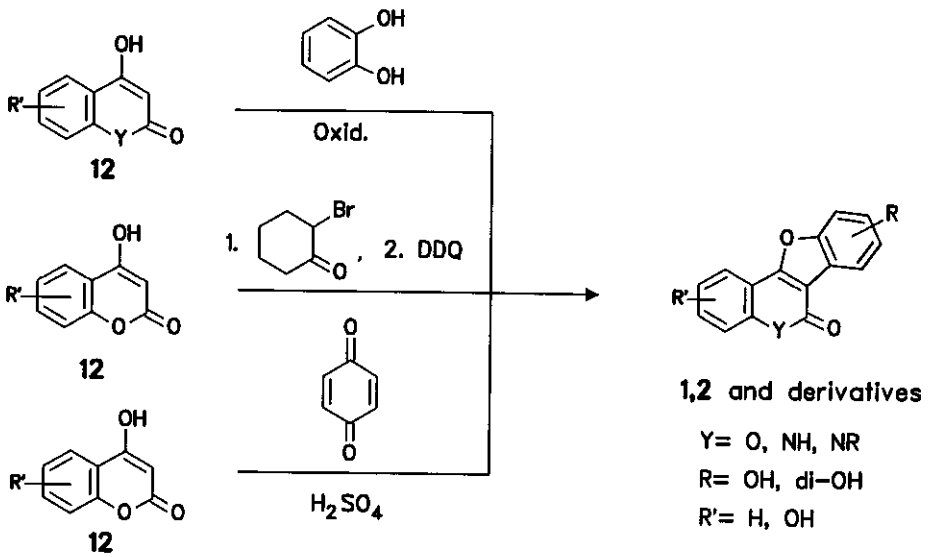
Fused ring systems, which contain both the indole and the quinoline nucleus, represent another type of natural products, the carboline ring system. Diazacoumestans correspond to the alkaloids of the 3,4-benzo-γ-carboline type, which are found *e.g.* in ibogamine[10] or are have pharmacological activity.[11]

2. A literature survey for synthetic pathways to coumestans and aza-coumestans

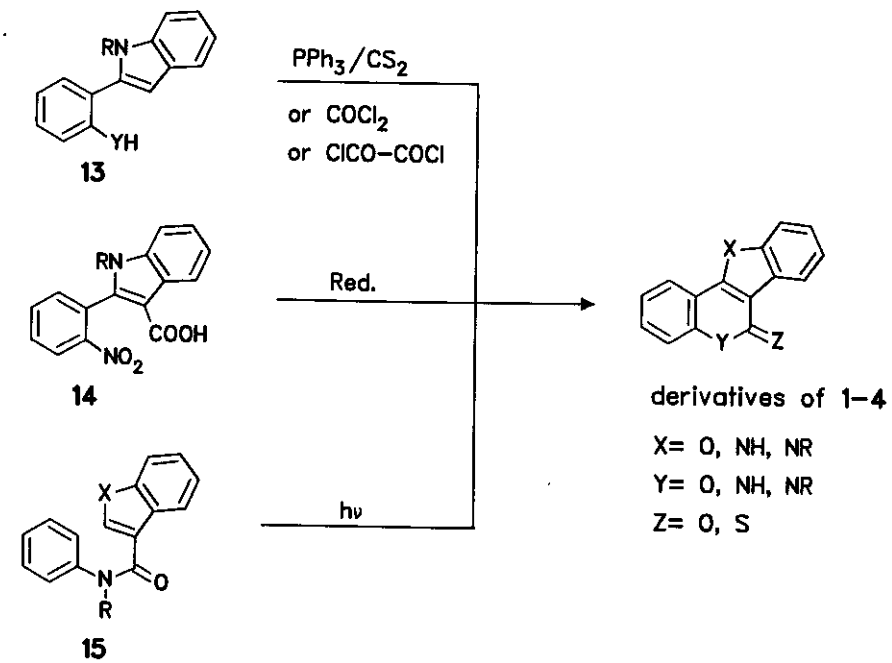
Synthetic methods found in the literature to afford coumestan and azacoumestan ring systems consist mainly of three kinds of cyclization reactions. One type is the formation of a single bond by the ring closure of 4-hydroxy- or 4-aminocoumarins and -quinolines (or precursors of these heterocycles) either 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] quinones[19] and related compounds.[20] Oxidation was performed either with inorganic oxidation agents (*e.g.* periodates), also electrochemical or enzymatic methods were used.



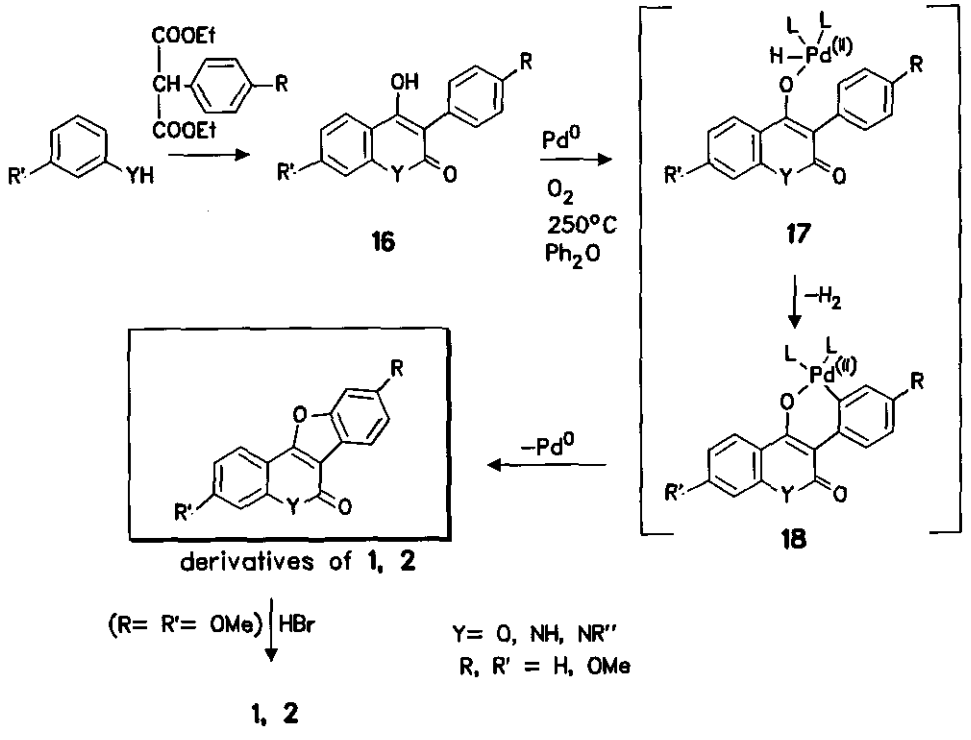
A further reaction sequence starts from benzofurans or indoles. So cyclization of 2-arylindoles (**13**) having an amino or hydroxy substituent in *ortho* position of the aryl ring can be cyclized using a C-1 building element.[21] A similar ring closure was reported using the corresponding 2-arylindol-3-carboxylates (**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 (Bryacarpenon-3).[26] A systematic study[27] 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 reactions[28] followed by an *ortho*-metallation step of the neighbouring phenyl ring to yield **18**. This six-membered palladium heterocylce (**18**) could react to the benzofuran (**1**, **2**) by the reductive palladium elimination step, which explains the strong dependence on the temperature.

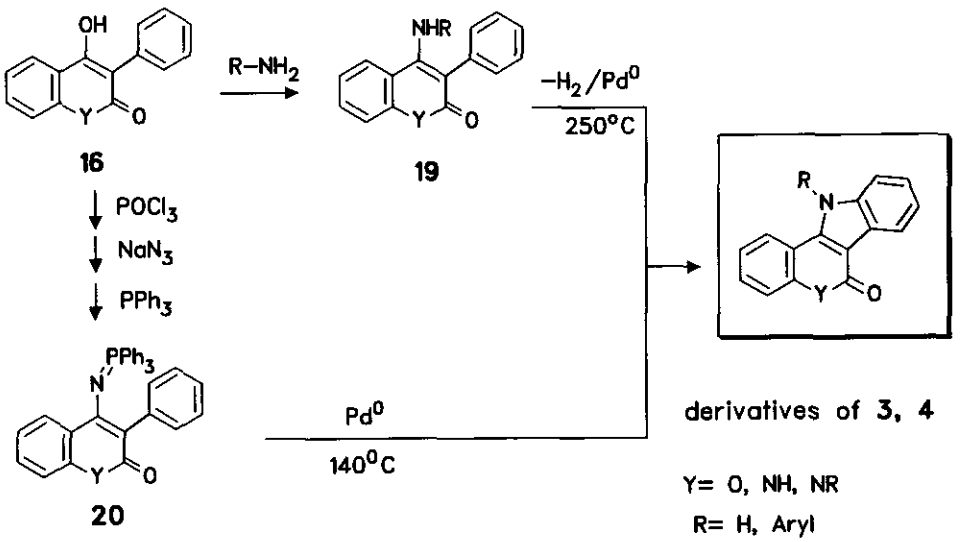
This considerations prompted us to experiment with Pd(II)-salts, which would not need the initial oxidation step. Actually, in this case the ring closure takes place in about 50% at temperatures of 60-80°C. By using the cooperation of oxygen the benzofurans (**1**, **2**) are obtained in purer form, 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 triarylbismuth* diacetates,[31] which avoids the synthesis of arylmalonates.

Whereas coumestrol dimethyl ether (**1**, Y= O, R= R'= OCH_3) 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 anilinocoumarins 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%.

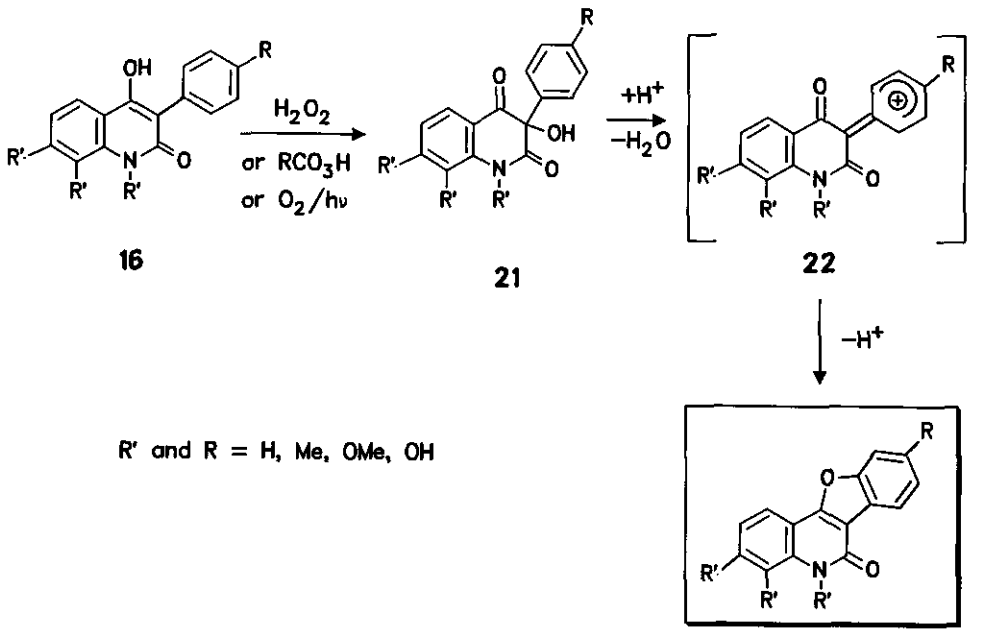
Alkylaminocoumarins and -quinolones (**19**, R= alkyl) did not cyclize to indoles (**3**, **4**). Either the alkyl group was cleaved to yield impure *N*-unsubstituted azacoumestans (**3**, **4**), or, in the case

of benzyl substituted (**19**) (R= $CH_2C_6H_5$) 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 Pd(0) as catalyst, the ring closure takes place to yield diazacoumestans (**4**) (Y= NH, NR) in 25% yields,[44] but difficult purification destroys any advantages of this reaction.

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

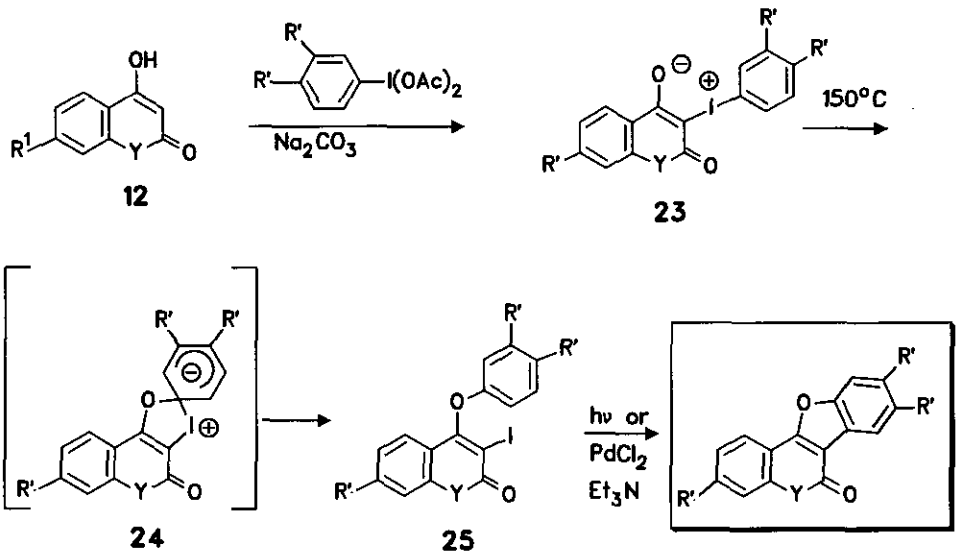
The starting materials, 3-aryl-3-hydroxy-2,4-dioxotetrahydroquinolines (**21**) are readily available by oxidation of 3-aryl-4-hydroxy-2-quinolones (**16**) with hydrogen peroxide in alkaline solution, peroxy acids such as 3-chloroperoxybenzoic acid or peracetic acid, by irradiation with uv light of 254 nm in the presence of oxygen[33] 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 applicated *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 benzopyran 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* form 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]

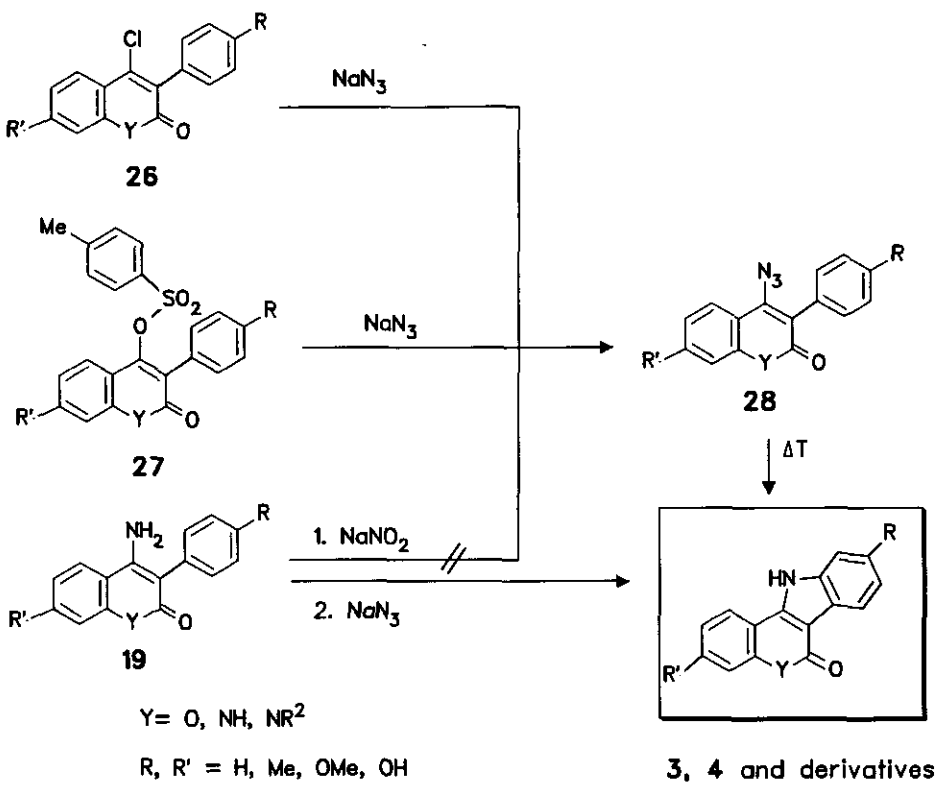
The photocyclization of the 3-iodo derivatives (**25**) (R'= H; Y= O, NH, NR) yields the coumestan or azacoumestan ring system of **1** or **2** in about 40%. Coumestan could also be obtained by photocyclization of 4-phenyloxycoumarin in the presence of iodine. With hydroxy or methoxyl groups at the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

These negative results prompted us to study the Ullmann[39] and Heck reaction[40] 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 systeme

From our studies, we excluded cylodehydrogenation reactions of 4-amino- or 4-triphenylphosphoranylideneaminocoumarins or -quinolones with methoxyl groups in the phenyl ring (R= OCH_3), 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]

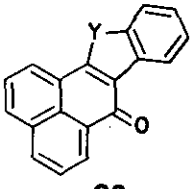


The azides (**28**) can be obtained either with sodium azide from the corresponding 4-chloro- or 4-tosyloxy compounds (**26**) or (**27**), respectively, which in turn could be obtained from the 4-hydroxy compounds (**16**) by chlorination with phosphoryl chloride or tosylation with tosyl chloride.[44]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

Application of suitable substituted azides (**28**) (R=R'=OCH_3) leads to the azacoumestrol derivatives (**3**) and (**4**), which can be converted into the receptor active azacoumestrols (R=R'=OH) by cleavage of the azacoumestrol ethers (R=R'=OCH_3) with hydrobromic acid.[46] In the quinolone series, we were not able to isolate the azide (**28**) (Y=NH, 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 diazacoumestrols (**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.



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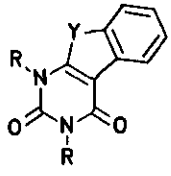

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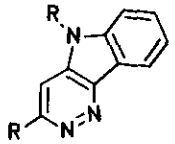

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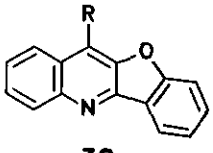

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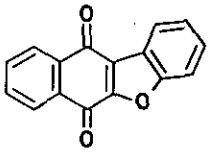

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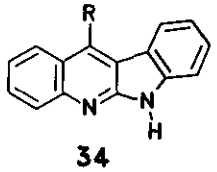

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2-Phenyl-3-hydroxy-1-phenalenones could be cyclized to afford benzofuran and indole ring systems of type (**29**),[25,47] 5-arylbarbituric acids underwent ring closure to benzofurans and indoles of type (**30**),[48] both by cyclodehydrogenation, cyclodehydration 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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