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HETEROANNELATIONS WITH *o*-AMINOALDEHYDES

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INTRODUCTION

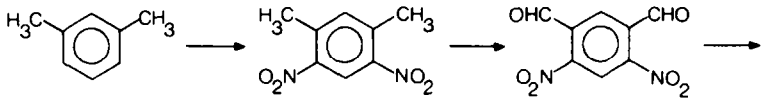
The formation of ring structures from *ortho*-substituted starting materials has very wide applicability for the annelation of heterocyclic systems and is often the method of choice for the elaboration of polycondensed materials composed of multiple fused rings. This construction method predetermines the direction of ring growth (angular *vs* linear) and generally permits the direct and regiospecific introduction of functional groups and/or substituents in the newly formed heterocyclic ring. Furthermore, it is usually compatible with the presence of functional groups in the starting material, which further enhances its synthetic potential.

Among numerous possibilities for *ortho*-joined functionalities those containing carbon and nitrogen are of particular importance, because the numerous combinations of their different oxidation states and easy accessibility of simple derivatives provide them with exceptional versatility in heteroannelation reactions. Their synthetic potential may be exemplified by the rich chemistry associated with the *o*-aminonitrile functionality, which gives entry into a large number of functionalized heterocyclic systems.[1] The utility of this combination is ultimately dependent on its facile elaboration from malononitrile or one of its simple derivatives. No such general synthetic method from acyclic starting materials is available for the *o*-aminoaldehyde functionality. Therefore, traditional methods for the elaboration of the individual functional groups must be performed on a preformed ring wherein the *ortho* relationship of the respective precursors must be ensured. This requirement is responsible for the unavailability of elaborated carbocyclic *o*-aminoaldehydes and for the slow growth of their heterocyclic counterparts. This inaccessibility has been widely reported in textbooks of heterocyclic chemistry, and this has resulted in a general lack of appreciation for their potential as synthetic intermediates, which is intrinsically greater than that of the *o*-aminonitrile combination. Furthermore, the instability of *o*-aminobenzaldehyde, the first and best known member of this class of compounds, has received considerable attention and is often cited as a further obstacle for their synthetic utility. That this instability, generally exaggerated,[2] and lack of synthetic entry are atypical of the general class may be seen from the large number of stable heterocyclic *o*-aminoaldehydes that have become accessible in recent years. Our findings that the aldehyde and amino functional groups can be generated simultaneously from readily available starting materials permits the full exploitation of their fascinating potential for the annelation of heterocyclic ring structures.

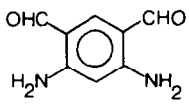
The chemistry of the *o*-aminoaldehyde functionality has not been reviewed previously, although some elements have appeared as part of reviews dealing with specific heterocyclic systems. The following sections discuss both the synthesis of *o*-aminoaldehydes, their remarkable versatility, and utility in the annelation of heterocyclic fused ring systems. This review follows the traditional division of carbocyclic and heterocyclic derivatives. This approach is necessitated by the disproportionally large amount of information available on carbocyclic systems, especially *o*-aminobenzaldehyde, as compared to their heterocyclic counterparts.

CARBOCYCLIC *o*-AMINOALDEHYDES

A general synthetic procedure for the elaboration of carbocyclic *o*-aminoaldehydes involves: nitration of a methyl aromatic compound, conversion of the methyl into the aldehyde group (frequently via a condensation/hydrolysis sequence with p-dimethylaminonitrosobenzene), and finally reduction of the nitro group. This sequence may be best illustrated by the synthesis of 4,6-diaminoisophthaldehyde **1** from *m*-xylene[3] (eqn 1). The choice of reducing agent is often critical. Ferrous sulfate and ammonia appears to be the most adequate reducing medium. Catalytic reduction has been employed successfully in a few specific cases,[4,5] although such reactions often stop well before the calculated amount of hydrogen is absorbed.[3,6] These reduction reactions are undoubtedly complicated by competing inter- and intra-molecular condensation reactions of the intermediate hydroxylamines. Reduction of *o*-nitrobenzaldehyde with an equimolar amount of ferrous sulfate resulted in the formation of 2,1-benzisoxazole (anthranil) **2** via the intermediate *o*-hydroxylaminobenzaldehyde[7] (eqn 2).



eqn 1



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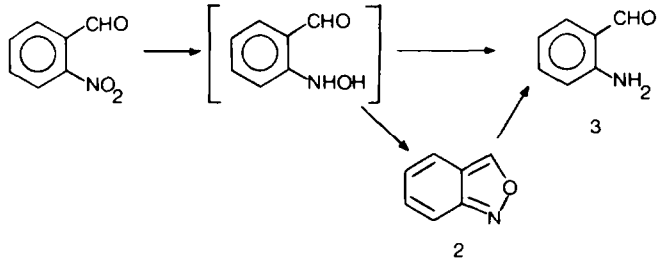


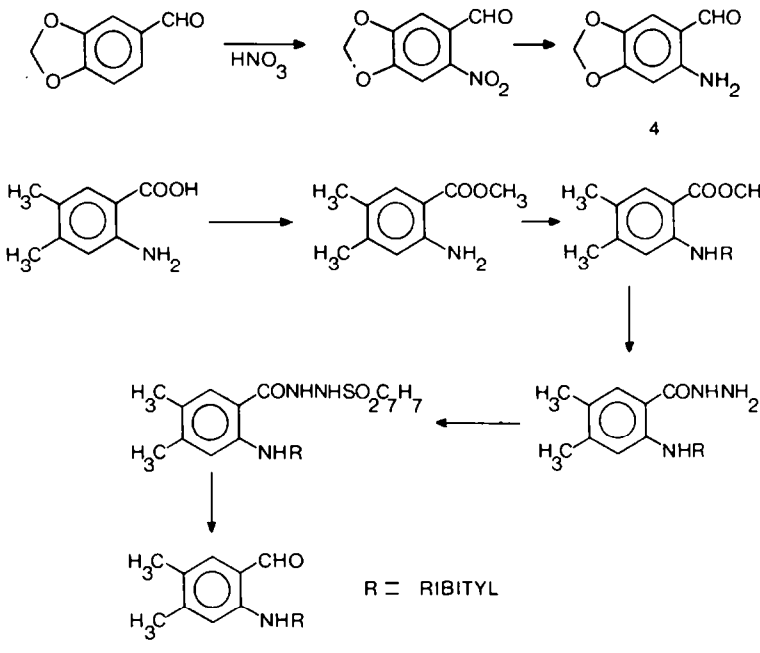
eqn 2

Further reduction of the isoxazole moiety gave *o*-aminobenzaldehyde **3**.[7,8] A detailed procedure for the preparation of *o*-aminobenzaldehyde **3** by ferrous sulfate reduction of *o*-nitrobenzaldehyde is available.[2,9] Difficulties encountered during reductions of *o*-nitroaldehydes may sometimes be alleviated by their prior conversion into *o*-nitroanils.[3,10] Selective reduction of a nitro group ortho to the aldehyde function may be accomplished with titanium(III) chloride, as illustrated by the synthesis of 2-amino-4-nitrobenzaldehyde in 60% yield from 2,4-dinitrobenzaldehyde[11] (eqn 3).

eqn 3

Direct nitration of aromatic aldehydes may be utilized if the meta directing influence of the aldehyde functionality is superseded by that of other substituents. This is illustrated by the high yield synthesis of 6-aminopiperonal **4**[6] (eqn 4). The number of substituted *o*-aminobenzaldehydes reported in the literature has not changed significantly since an earlier count[12] of eight mono- and fourteen di- and tri-substituted derivatives in a paper published in 1958.

An alternative less widely employed synthesis is the conversion of *o*-aminocarboxylic acids into the corresponding *o*-aminoaldehydes via the McFayden-Stevens procedure.[13] This method is particularly well suited for the synthesis of *N*-alkylated *o*-aminobenzaldehydes as illustrated for the conversion of 4,5-dimethylanthranilic acid into 2-*N*-ribitylamino-4,5-dimethylbenzaldehyde **5**, a key component in the synthesis of 5-deazariboflavin[14] (eqn 5).

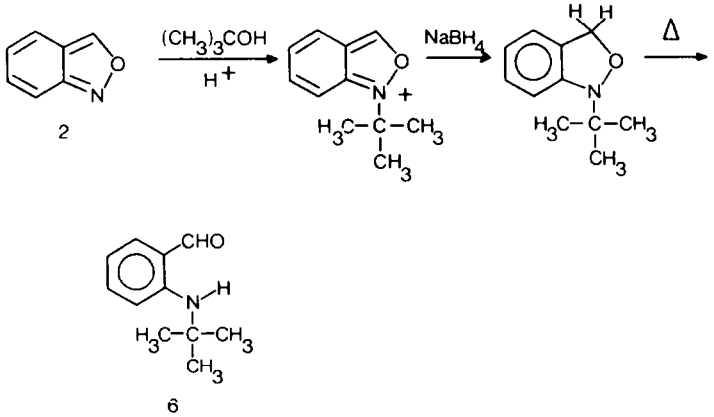


eqn 4

eqn 5

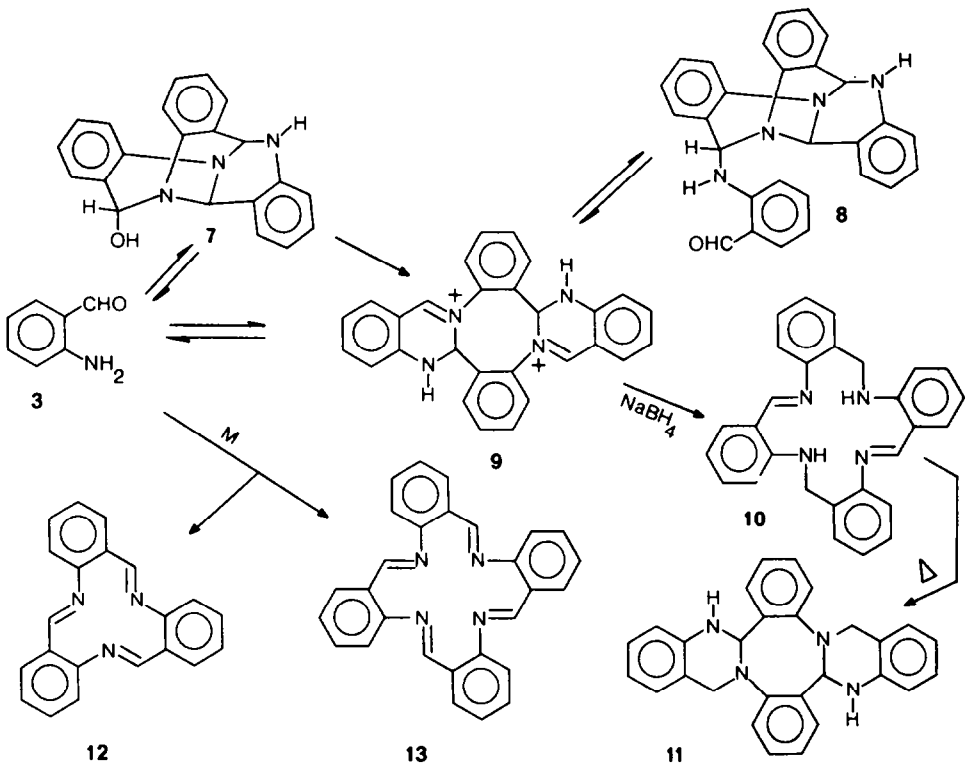
The facile hydrogenolysis of the isoxazole moiety of anthranils **2** offers the opportunity to use this heterocyclic system for the construction of elaborated *o*-aminoaldehydes. The synthetic utility of numerous heterocycles as vehicle for the generation and transformation of functional groups is well documented,[15] but remains virtually unexplored for the anthranil → *o*-aminoaldehyde conversion. The synthesis of 2-*N*-*t*-butylaminobenzaldehyde **6** illustrates this synthetic strategy[16] (eqn 6).

Finally, it is noteworthy that specific *ortho* formylation of aniline *via* a boron heterocycle did not result in the formation of *o*-aminobenzaldehyde, although the method is successful for the conversion of *N*-methylaniline into 2-*N*-methylaminobenzaldehyde.[17]



eqn 6

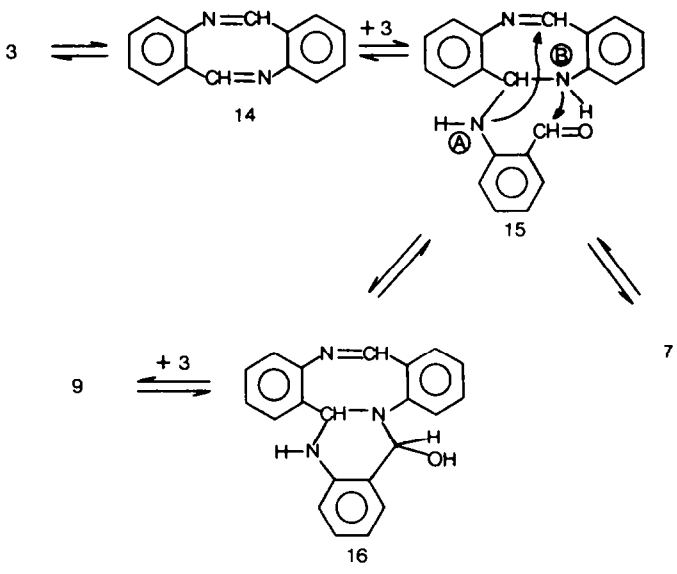
The tendency of *o*-aminobenzaldehydes to form "polymeric" products upon standing and especially when treated with acids has received wide attention and is often regarded as an intrinsic feature of this functional group. Reliable quantitative data for their stability when stored are only available for the parent compound, which may be recovered in 60 and 40 % after one and two months at 20°. At 5° there was no change in this time.[18] The number and nature of the self-condensation products of *o*-aminobenzaldehyde **3** have received considerable attention since their original description nearly a century ago (Scheme 1). Treatment of **3** with dilute acid at room temperature rapidly formed a crystalline precipitate for which analysis supported a bisanhydro trimer formulation. Spectroscopic and chemical evidence have firmly established the tricyclic structure **7** for this product,[18,19] which was found to be in equilibrium with the monomeric species below pH 3. A



Scheme 1.

second condensation product was obtained by the action of strong acid upon **3** followed by basification[18] or treatment with water[19] of the red crystalline precipitate (see below) obtained from the acid medium. The resulting pale yellow crystalline product was formulated as a trisanhydro tetramer for which spectroscopic data and chemical evidence have confirmed tricyclic structure **8**.[18,19] The trimeric species **7** was converted into tetramer **8** upon treatment with strong acid (via the red salt), although it remained unchanged when reacted with **3** at pH 4. The self-condensation product obtained from **3** upon storage at room temperature was found to be the bisanhydro trimer **7**, identical in all respects with the product obtained from dilute acid. A quite different structure must be at hand in the red salt from which trisanhydro tetramer **8** was obtained upon neutralization. Spectroscopic data clearly revealed the presence of the azomethinium linkage in the former and the absence of C=N linkages in the latter. It follows therefore that the salt is not simply the conjugate acid of tetramer **8**. Analytical data obtained on the hydrochloride salt led to the conclusion that one molecule of water was incorporated, and a bicyclic hydrogen bonded structure containing an alcohol function was proposed to accommodate the combustion data.[18]

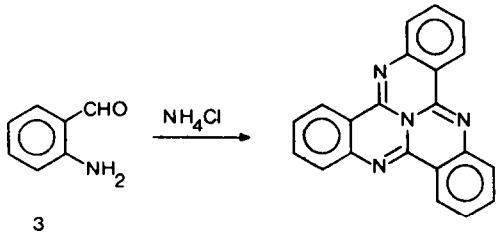
However, a more extended series of red salts derived from **3** (fluoborate, trifluoromethylsulfonate, perchlorate, sulfate) were found to analyze correctly as anhydrous salts of well defined molecular composition, unlike the hydrochloride which was found to form lattice compounds of complicated stoichiometry.[20] Spectral comparison with the hydrochloride clearly established that the elements of water were present as lattice water and not as an alcohol functional group. The red salts obtained from **3** upon treatment with strong acid must be formulated therefore as diacid salts of the tetrakisanhydro tetramer of *o*-aminobenzaldehyde, for which the tricyclic structure **9** containing an eight membered ring was proposed. Preliminary X-ray analysis on the trifluoromethylsulfonate salt supports this structural assignment.[20] Comparison of tetramer salt **9** with neutral tetramer **8** reveals the extraordinary reorganization of the molecular framework caused by simple treatment of **9** with water. The reaction of **9** with nickel salts provides insight into the mode of bond reordering in transformations of the tetramer salts. It was found that treatment of **9** with nickel acetate gave only the tetrameric nickel complex, rather than the mixture of trimeric and tetrameric nickel complexes obtained from *o*-aminobenzaldehyde and nickel salts (see below). This requires that bond breaking only takes place in the inner ring while the outer ring remains intact and also precludes a



Scheme 2.

depolymerization reaction to *o*-aminobenzaldehyde. This mode of bond breaking was also substantiated by reduction of **9** with sodium borohydride which gave the macrocyclic compound **10**. It is interesting to note that this reduced macrocycle was isomerized to its thermodynamically more stable isomer **11**, identical in ring size with the tetramer salt **9**.

The complexity of these rearrangements is further illustrated by the facile conversion of trimer **7** and neutral tetramer **8** into tetramer salt **9** in the presence of strong acid. It was also observed that a dilute, acid solution of **9** was slowly depolymerized with reformation of **3**.[18] It will be noted that the bisanhydro dimer, dibenzo[*b*,*f*][1,5]diazocine **14** is conspicuously absent from the series of self-condensation products of *o*-aminobenzaldehyde, although it is accessible by a different synthetic route.[21] It seems likely therefore that **14** is formed as a reactive intermediate and could play a critical role in determining the ultimate outcome of the self-condensation of **3** (Scheme 2). Thus, nucleophilic attack of the amino function of **3** on an azomethine group of **14** would result in the addition product **15**. Inspection of **15** reveals the presence of two amino groups (A) and (B) of nearly identical constitution and two appropriately positioned electrophilic sites. These structural features permit two distinct competitive pathways for further reaction: transannular addition of amine (A) to the remaining azomethine group followed by the addition of amino group (B) to the aldehyde results in the formation of trimer **7**. Alternatively, if amino group (B) reacts first with the aldehyde, then transannular reaction of amine (A) is no longer geometrically possible and the remaining azomethine is free to react with an additional molecule of *o*-aminobenzaldehyde. The fate of carbinolamine **16** will be determined by the acidity of the reaction medium. In strong acid, protonation followed by loss of water gives an azomethinium ion, which after addition of another molecule of **3** precipitates from the reaction mixture as the diacid tetramer salt **9**, effectively shifting the equilibria with exclusive formation of the tetrameric species. In dilute acid, on the other hand, azomethinium ion formation is not possible and the equilibrium **15** $\rightleftharpoons$ **16** is shifted towards the exclusive formation of **7**, again by precipitation from the reaction medium.



eqn 7

Still other self-condensation products are obtained when *o*-aminobenzaldehyde is treated with certain metal ions in alcoholic solvents (Scheme 1). These reactions lead to the formation of the coordinated tetradentate Schiff base macrocylic ligand **13** and/or tridentate ligand **12** and provide one of the best examples of metal ion template reactions.[22] In the presence of copper(II), *o*-aminobenzaldehyde formed the coordinated tetradentate ligand[23] **13**; in the presence of the oxovanadium(IV) ion the tridentate ligand **12** was obtained exclusively.[24] Reaction with Ni(II) ions gave a mixture of the coordinated ligands **12** and **13**.[23] The same complexes are also accessible from the neutral trimer **7** as well as from the tetramer salts **9**.[20] Once again the specificity of the metal ion induced molecular reorganizations is to be noted.

Finally, in connection with the self-condensation reactions of *o*-aminobenzaldehyde, it should be mentioned that treatment of **3** with ammonium chloride at 230°C resulted in the formation (16%) of a mixed trimeric product, tricycloquinazoline[26] **17**, which is, however, more readily accessible via the trimerization of *o*-aminobenzonitrile[27] (eqn 7).

No detailed studies on the self-condensation products of ring substituted *o*-aminobenzaldehydes are available. Their instability and tendency to form condensation products are poorly documented, and even a qualitative assessment of the effect of substituents on their stability is not possible with the information at hand. The increased stability of 2-amino-3,5-dimethylbenzaldehyde with respect to the parent compound **3** has been noted[28] and is undoubtedly due to steric hindrance at the amino group. It should be pointed out that ring substituted *o*-aminobenzaldehydes were often not isolated but used immediately following their generation (see, e.g. Refs. 4, 5, 14, 29). Their "polymeric" products may be used successfully for ring annelations.[29] *N*-Alkyl substituted *o*-aminobenzaldehydes are likewise unstable in acid medium; the structure of the dimeric product was established for the self-condensation of 2-*N*-methylaminobenzaldehyde.[30]

HETEROANNELATIONS WITH CARBOCYCLIC *o*-AMINOALDEHYDES

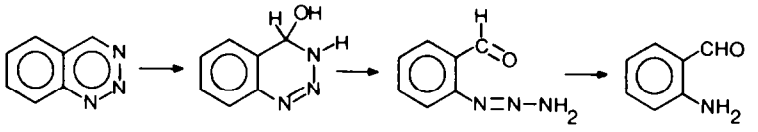
Heteroannelation reactions with *o*-aminoaldehydes may be classified according to the number of carbon atoms supplied to the newly created ring by the annelating reactant. For 6-membered rings one can thus incorporate zero, one or two carbon atoms, with remaining positions occupied by suitable heteroatoms.

Carbocyclic *o*-aminoaldehydes undergo the typical reactions of the aldehyde and amine functional groups. Intramolecular ring closure of some of their derivatives has been investigated intensively as a route to the unsubstituted 1,2,3-benzotriazine system **18** (Scheme 3). An attractive synthetic strategy

3 18 eqn 8

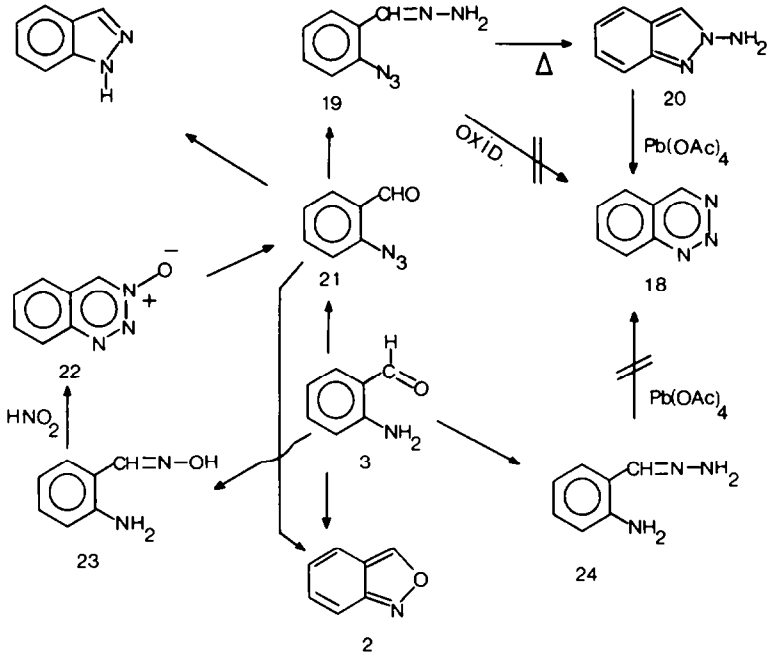
for the conversion **3** → **18** would involve formation of amino-hydrazone **24** and oxidative removal of hydrogen from the two terminal NH_2-groups. However, oxidation of **24** with lead tetraacetate gave only tars from which **18** could not be isolated.[31] An alternative mode of cyclization via decomposition of an *o*-diazoazide also resulted in an intractable mixture of products. The diazoazide was prepared from *o*-azidobenzaldehyde **21**, available from the diazonium salt of **3** and sodium azide, via its conversion into the hydrazone **19** with hydrazine at room temperature and iodine catalysis, and oxidation of **19** with mercury(II) oxide. Reaction of **21** with hydrazine under standard hydrazone formation conditions led to indazole in 87% yield. It should be noted that oxidation of amino hydrazones, derived from *o*-aminoketones, resulted in the formation of 4-substituted 1,2,3-benzotriazines in fair to excellent yield.[31] Unsubstituted **18** was finally obtained in low yield via lead tetraacetate oxidation of 1- or 2-aminoindazole **20** under careful exclusion of water.[31] 1,2,3-Benzotriazine **18** is a very reactive compound towards nucleophiles, and this explains why it cannot be isolated through the above-mentioned oxidative methods. Solutions of **18** in dilute acid are rapidly and quantitatively transformed in *o*-aminobenzaldehyde, most likely via covalent hydration across the 3,4-bond (eqn 9). The important relationship of covalent hydration of some heterocyclic systems and *o*-aminoaldehydes will be discussed in a later section.

Diazotation of *o*-aminobenzaldehyde oxime **23** results in the formation of an intramolecular coupling product, for which the structure of 1,2,3-benzotriazine-3-oxide **22** has been proposed in



18 3 eqn 9

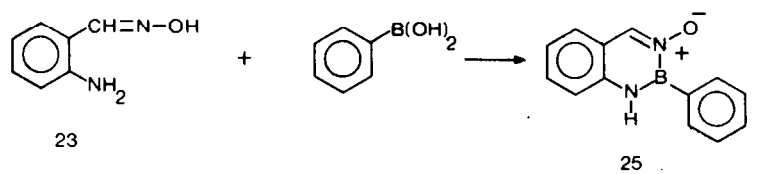
analogy with the similar diazotation products obtained from *o*-aminoketone oximes.[32] Their facile conversion by boiling water or alkali into *o*-azidobenzaldehyde **21** may be readily explained as above by covalent hydration or nucleophilic attack across the 3,4-bond of the 1,2,3-benzotriazine heterocycle. An earlier formulation[33] of the intramolecular coupling product **22** as 3-oximinoindazole was later revived[34] and it was argued that the indazole formulation could be the product of the diazotation in acid medium which, upon treatment with water or alkali, would isomerize to the 1,2,3-benzotriazine-3-oxide structure. It seems, however, that steric and electronic differences between aldehydes and ketones (and their oximes) are not sufficiently large to account for such a drastic change in coupling products between *o*-aminocarbonyl oximes. This is substantiated by the similarity of the ultraviolet spectra of **22** and the diazotation product obtained from *o*-aminoacetophenone oxime.[168] Application of the diazotation reaction to 2-amino-3,5-dimethyl and 2-amino-3,6-dichlorobenzaldehyde proceeded much better than the reaction of the parent compound.[32]



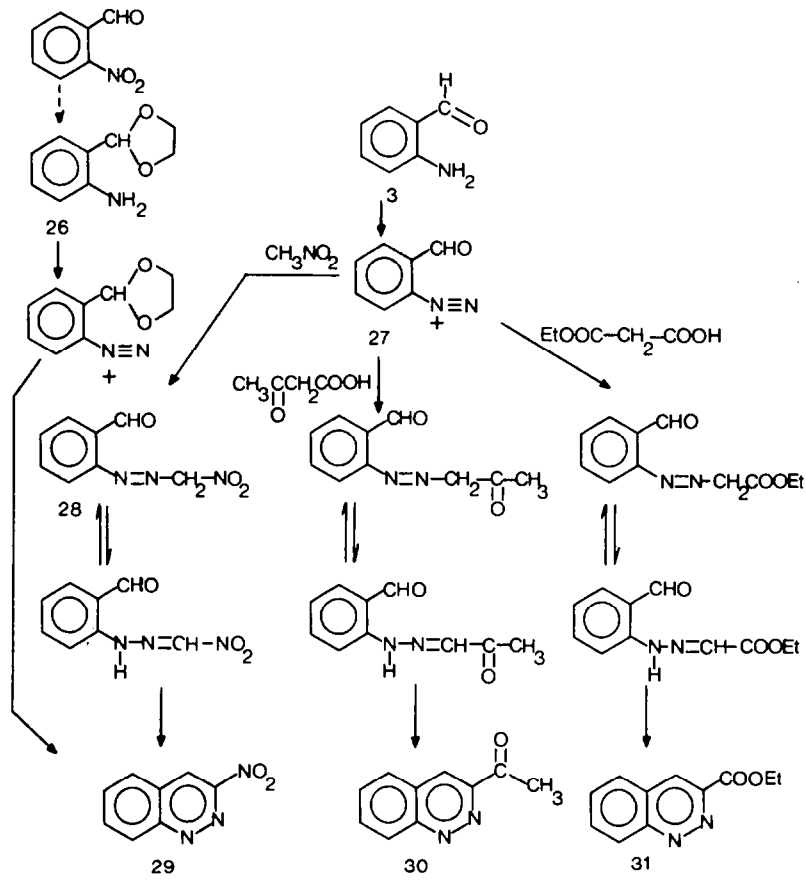
Scheme 3.

The reduction of 2,1-benzisoxazole **2** to *o*-aminobenzaldehyde **3** was described earlier. The reverse process **3** → **2** may be carried out by oxidation with Caro's acid or hydrogen peroxide,[8] a procedure of little synthetic utility. 2,1-Benzisoxazole is also available via decomposition of *o*-azidobenzaldehyde **21**.[35]

Annelation of **23** may also be used for the incorporation of other heteroatoms. Thus, reaction of **23** with benzeneboronic acid[36] gave the boron heterocycle **25** (eqn 10).

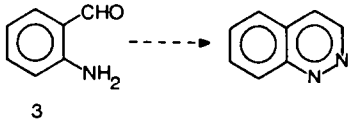


23 25 eqn 10



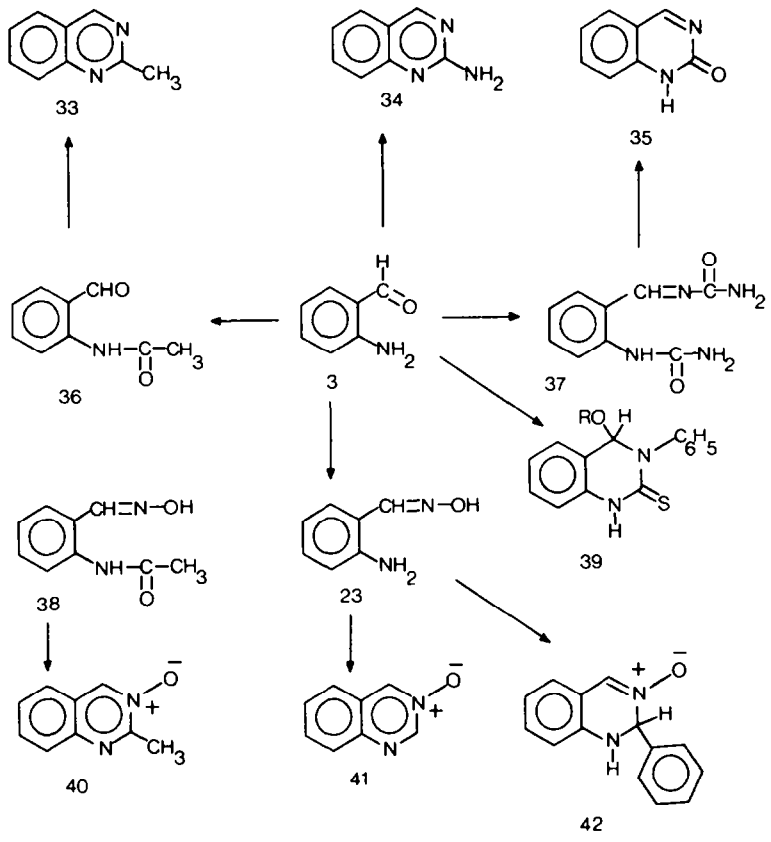
Scheme 4.

Annelation reactions of the *o*-aminoaldehyde function accompanied by the incorporation of one carbon atom derived from the annelating reagent can lead to the cinnoline, quinazoline, and indole heterocyclic systems.

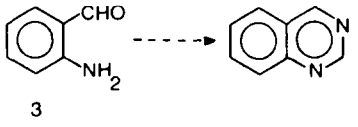


eqn 11

The cinnoline ring system may be constructed via the diazonium salts of aromatic *o*-aminoaldehydes. Their coupling with CH-acidic compounds provides intermediate products, which may be ring-closed by aldol-type condensations of the aldehyde with the newly introduced activated carbon atom (Scheme 4). Thus, coupling of diazonium salt **27** with nitromethane under rather unique diazotation conditions gave nitroformaldehyde-*o*-formylphenylhydrazone (or its azotautomer) **28** in 53–67% yield.[37] Ring closure to 3-nitrocinnoline **29** could be effected with dilute sodium hydroxide (40%), activated aluminium oxide[37] (40%), or best with an anion exchange resin[12] (55%). Extension of this sequence to 2-amino-4-chloro- and 2-amino-5-chlorobenzaldehyde and 6-aminopiperonal gave the corresponding 3-nitrocinnolines in 15% yield, based on the starting *o*-nitrobenzaldehydes (the substituted *o*-aminobenzaldehydes were not isolated). Much better overall yields were obtained by protection of the aldehyde group via its ethylene acetal during the diazotation/coupling reaction.[12] *o*-Nitrobenzaldehyde was converted into its ethylene acetal; its reduction gave *o*-aminobenzaldehyde ethylene acetal **26** (not isolated), which was immediately diazotized and coupled with nitromethane to give **29** in 69–84% yield after removal of the protecting group. Extension of the coupling reaction of **27** with carbon acids such as acetoacetic acid and ethyl hydrogen malonate gave 3-acetylcinnoline **30** and 3-carbethoxycinnoline **31** in 20% and 10%, respectively.[38]



Scheme 5.

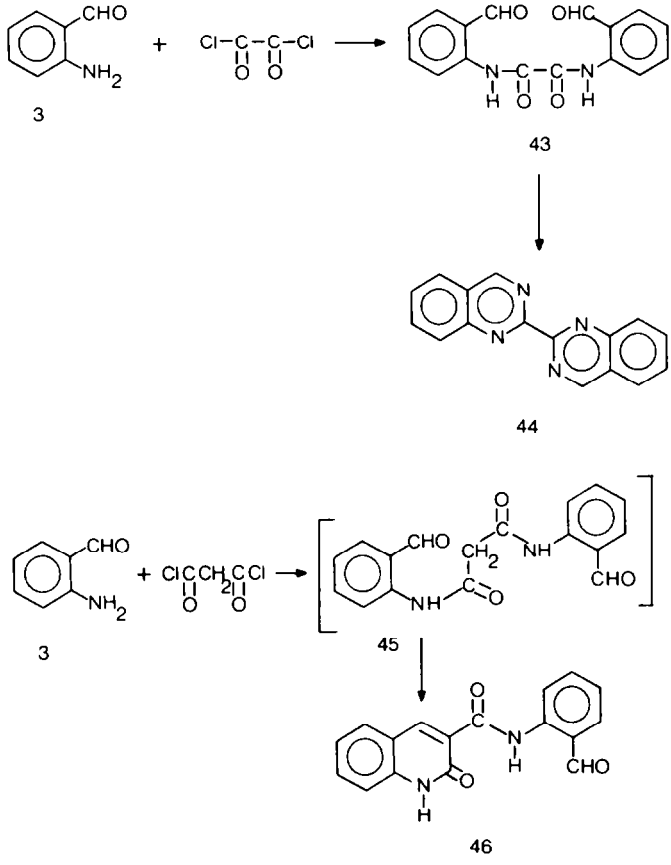


eqn 12

The quinazoline ring system[39] is accessible from *o*-aminoaldehydes either via stepwise incorporation of the carbon and nitrogen fragments needed for completion of the pyrimidine moiety or by their combined introduction in one reaction step (Scheme 5). In the latter procedure both elements are delivered by a single reactant. Thus, treatment of **3** with guanidine carbonate in refluxing decalin gave 2-aminoquinazoline **34** in nearly quantitative yield.[40] Application of this reaction to several ring substituted *o*-aminobenzaldehydes gave substituted 2-aminoquinazolines, although in much lower yield.[29] However, these *o*-aminoaldehydes were not purified but used immediately as obtained from the reduction of the starting *o*-nitroaldehydes. It was also noted that even their "polymeric" products could be used in the reaction with guanidine carbonate. Melt reaction of **3** with excess urea provides a direct route to 2-quinazolone **35**.[41] This apparently straightforward reaction is more complex than generally believed. It was found that formation of **35** is a two-stage process; reaction of **3** with urea resulted in the formation of a product which did not analyze for the quinazolone structure and was formulated as *o*-ureidobenzylidine urea **37**. Acid washing of this product (as in the original synthetic procedure[41]) or treatment with base gave **35** with elimination of urea.[42] Reaction of **3** with phenyl isothiocyanate in ethanol resulted in the formation of 3-phenyl-4-ethoxy-2-thio-3,4-dihydroquinazolone **39**, a colorless solid, which dissolves in strong acid with brilliant red color;[43] it also displays thermochromic behavior in inert solvents.[44]

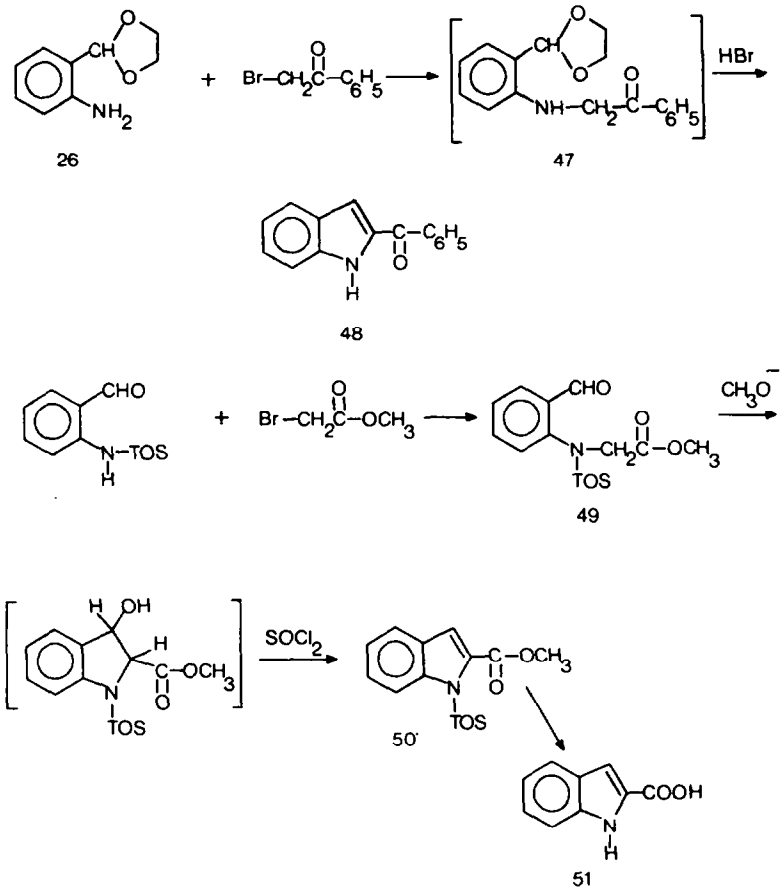
Two synthetic methods can be employed for the stepwise completion of the pyrimidine moiety of the quinazoline system. Ring closure with ammonia on a preformed acylated *o*-aminobenzaldehyde offers a general method for the synthesis of 2-substituted quinazolines. Acetylation of **3** with acetic anhydride gave **36**, which upon treatment with ammonia in alcohol was transformed in 2-

methylquinazoline **33** in 94% yield.[45] Similarly prepared were 2-ethyl-, 2-propyl-, and 2-phenylquinazoline. The synthetic utility of this sequence may be further illustrated by the facile synthesis of 2,2'-diquinazolinyl **44** via the reaction of **3** with oxalyl chloride and treatment of the resulting *N,N*-di(*o*-formylphenyl)oxanilide **43** with ethanolic ammonia.[46] The similar reaction of **3** with malonyl chloride did not give the malonamide analog of **43** but resulted in the formation of the 2-quinolone derivative **46**[47] (eqn 13). It is clear that the presence of a doubly activated methylene group in the intermediate **45** is responsible for its spontaneous ring closure to **46**. With somewhat less activated methylene groups a mixture of open chain amide and 2-quinolone was formed, as found in the acylation of **3** with phenylacetyl chloride.[45] Acylated *o*-aminoaldehydes, such as **36**, containing no additional activation of their α-methylene group may be converted into 2-quinolones upon treatment with base (see further). Treatment of **3** with dimethylmalonyl chloride gave only trimer **7**.[47] Apparently amidation is greatly retarded by steric hindrance and **3** is more rapidly consumed by the formation of the trimeric product.

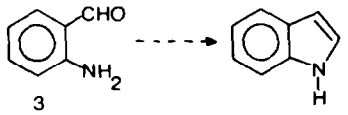


eqn 13

The alternative two step quinazoline synthesis starts from *o*-aminobenzaldehyde oxime **23** (Scheme 5). Conversion into **38** with acetic anhydride, followed by treatment with strong acid gave 2-methylquinazoline-3-oxide[48] **40** rather than the indazole or benzodiazepin ring systems as previously formulated. This reaction has been the subject of considerable controversy.[49] Acylation with other anhydrides or acid chlorides[50] likewise gives 2-substituted quinazoline-3-oxides, although they were formulated differently in the original literature. The versatile synthetic intermediate 2-chloromethylquinazoline-3-oxide is accessible from **23** by a similar reaction sequence.[51] Unsubstituted quinazoline-3-oxide **41** may be synthesized from **23** and ethyl orthoformate in very high yield.[52] The reaction product of **23** with benzaldehyde[50] may be formulated as 1,2-dihydroquinazoline-3-oxide **42** in analogy with the reaction of aldehydes and *o*-aminoketoximes.[53] Finally, this method of quinazoline synthesis has been investigated intensively in the case of *o*-aminoketones, because of their conversion into analogues of the sedative Librium.[49]

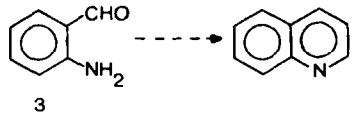


Scheme 6.



eqn 14

Conversion of carbocyclic *o*-aminoaldehydes into the indole system requires the addition of one carbon atom during the ring formation reaction. This may be achieved via *N*-alkylation with activated halides followed by intramolecular aldol condensation (Scheme 6). Direct alkylation of **3** with α-bromoketones however did not result in the formation of the indole skeleton but gave only tarry intractable products. When **3** was replaced by the ethylene acetal **26**, alkylation with phenacylbromide proceeded readily with formation of the intermediate **47**, which was immediately treated with HBr to give 2-benzoylindole **48** in 60% overall yield.[54] Introduction of the *N*-sulphonyl group in **3** allowed the direct alkylation of the amino group with methyl bromoacetate to give **49** in very high yield. This sulfonamide was readily ring closed with base and upon dehydration with thionyl chloride gave indole **50**. Removal of the tosyl group was accompanied by hydrolysis of the ester group with formation of indole-2-carboxylic acid **51**.[55]



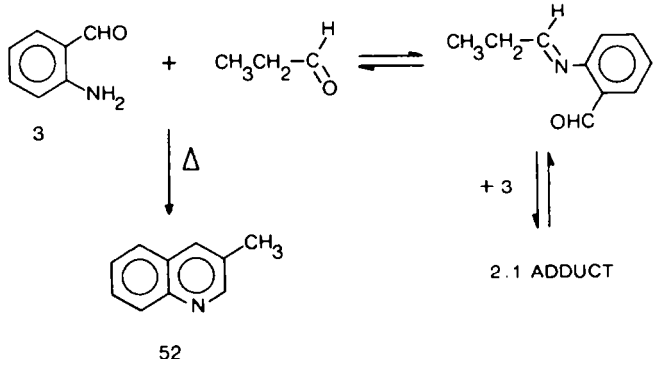
eqn 15

The quinoline ring system is accessible from the *o*-aminoaldehyde functionality via the addition of two carbon atoms during ring formation. The presence of both a nucleophilic and electrophilic center in *o*-aminobenzaldehydes requires a matching pair of such sites in the annelating reactant for bond formation and ring closure.

These requirements may be met by a group of CH-acidic compounds where activation of an α-methylene group is achieved by electron withdrawing groups capable of undergoing nucleophilic addition reactions with an aromatic amine. Carbon–carbon bond formation, via such carbanionic species, is one of the most useful synthetic reactions, and it is not surprising therefore that their combination with *o*-aminoaldehydes constitutes an exceptionally versatile annelation reaction. The following sections will discuss ring closure reactions with annelating reactants possessing different electrophilic sites responsible for α-methylene activation.

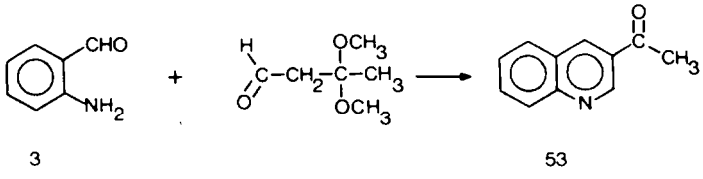
The reaction of *o*-aminobenzaldehydes with aldehydes and ketones provides access to quinolines, substituted on the pyridine nucleus, and is generally known as Friedländer quinoline synthesis. A review of this condensation reaction has appeared as part of a survey on the synthesis of this heterocyclic system, although it is not focused on the chemistry of *o*-aminoaldehydes.[56] Representative examples of this condensation reaction with aliphatic and aromatic ketones are illustrated in Schemes 7–9, 11–13. Friedländer condensations are generally carried out either with base catalysis (sodium or potassium hydroxide, sodium alkoxides, piperidine) in water or alcoholic solvents or by heating a mixture of the components in the absence of solvent. Acid catalysis, modeled after its use in condensation with *o*-aminoketones,[57–59] (sulphuric acid in acetic acid or anhydrous hydrochloric acid in ethanol) has been applied successfully to Friedländer condensations of *o*-aminobenzaldehyde,[60–73] and appears to offer considerable advantages over the traditional base-catalyzed method (see below), although its general applicability remains to be demonstrated. An interesting condensation procedure employing ion exchange resins has been described[74] but has received no further attention.

Aliphatic aldehydes do not react satisfactorily with *o*-aminobenzaldehydes under base-catalyzed conditions. Although acetaldehyde and **3** gave quinoline[7] (unreported yield), its reaction with 6-aminopiperonal **4** did not result in the formation of the quinoline nucleus.[10a] *o*-Aminoaldehydes are therefore unsuitable for the direct preparation of quinolines, which are unsubstituted on the pyridine ring. The complexity of their reactions with aliphatic aldehydes may be illustrated by the reaction of **3** with propionaldehyde. A neat mixture of the two compounds resulted in the formation of a crystalline compound, for which analysis is indicative of a condensation product derived from 1 mol of propionaldehyde and 2 moles of **3**[75] (eqn 16). Although its structure was not determined, its formation most likely results from Schiff base formation followed by addition of a second molecule of **3** across the azomethine bond.

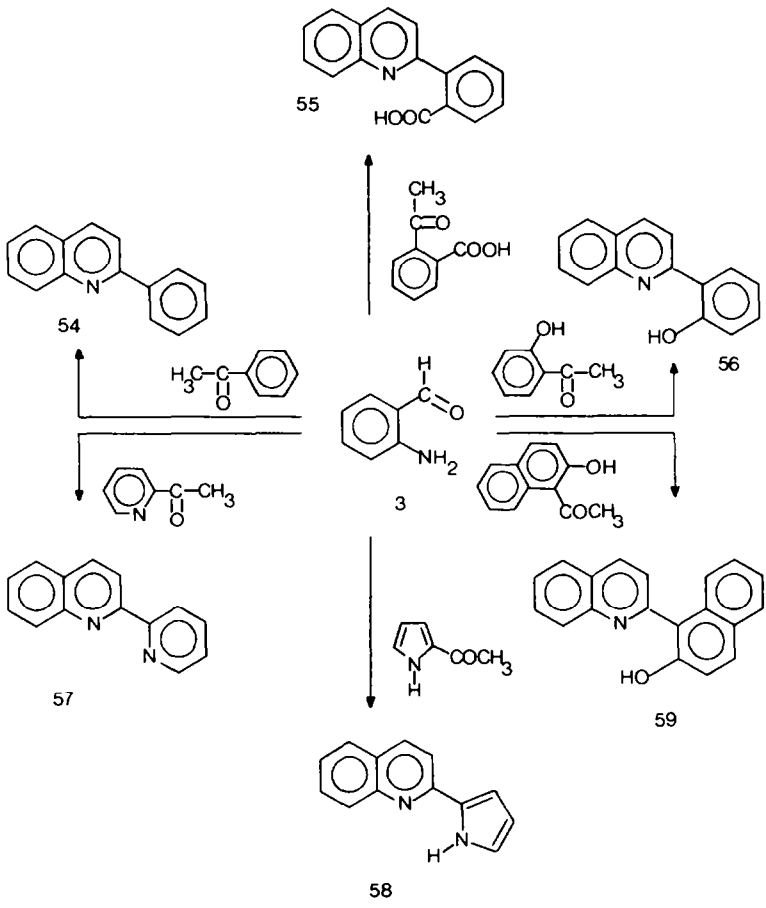


eqn 16

Base-catalyzed condensation did not result in the formation of 3-methylquinoline **52** but gave an intermediate oily product of undetermined structure, which was partly converted into **52** upon distillation. A neat mixture of **3** and propionaldehyde heated to 220° gave **52** in 80% yield.[75] Reaction of **3** with 3,3-dimethoxybutyraldehyde in the presence of the ion exchange resin Amberlite IRA-400 in refluxing methanol gave 3-acetylquinoline **53** in 50% yield[74] (eqn 17).



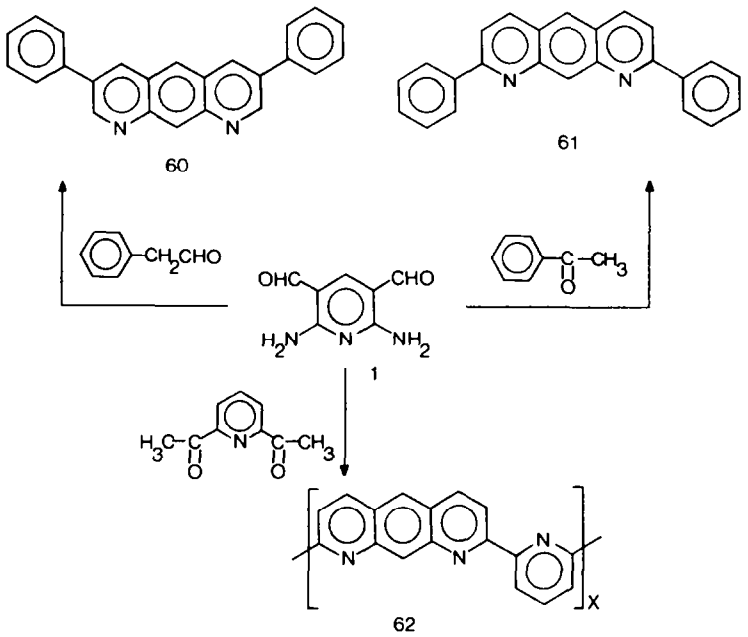
eqn 17



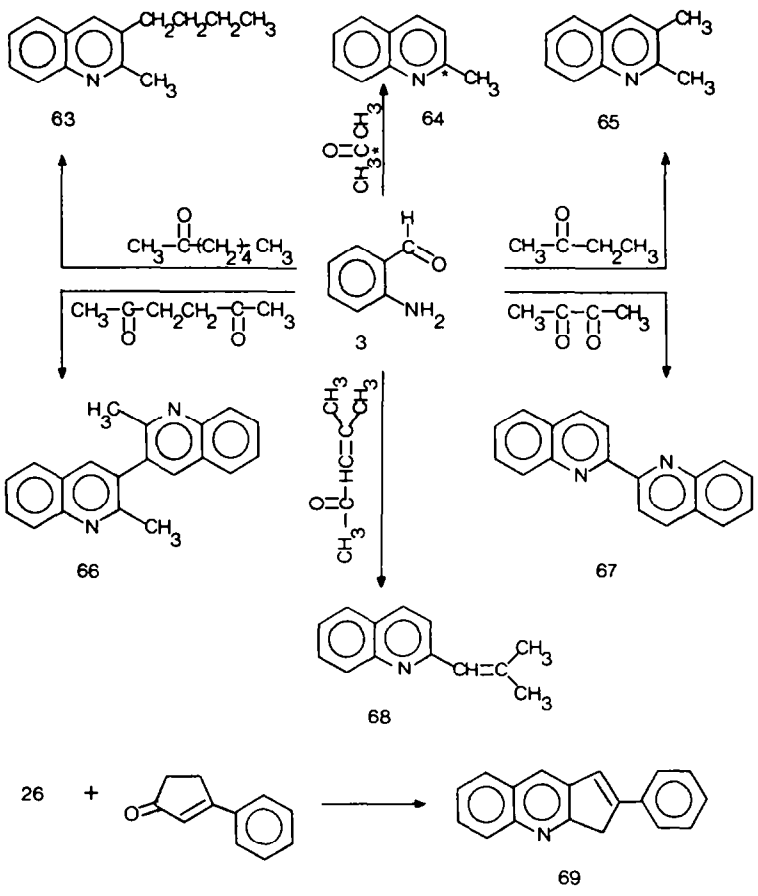
Scheme 7.

Base-catalyzed reactions with aromatic and aliphatic ketones, on the other hand, may be carried out successfully, and a large number of such condensation reactions have been reported. Acetyl aromatic ketones are readily transformed into 2-arylquinolines (Scheme 7). Thus, base-catalyzed condensation of **3** with acetophenone gave 2-phenylquinoline **54**.[74,76] Very few substituted acetophenones have been condensed with *o*-aminoaldehydes, and it is not possible therefore to evaluate steric and electronic effects on their condensation reactions. The interesting quinoline derivative **56** was prepared in 60% yield from 2-hydroxyacetophenone and **3**, which reacted similarly with the 3- and 4-hydroxy isomers.[77] The homologous naphthyl derivative **59** was obtained from 1-acetyl-2-hydroxynaphthalene in unreported yield.[78] Dihydroxyacetophenone, on the other hand, did not react with *o*-aminobenzaldehyde.[79] Reaction of **3** with *o*-acetylbenzoic acid[80] permits the introduction of a carboxylic acid group *ortho* to the quinoline moiety of 2-arylquinolines, **55**. Condensation with 2-acetylpyridine[81,82] and 2-acetylpyrrole[82] gave the heterocyclic substituted quinolines **57** and **58**, respectively. Contrary to an earlier report,[79] deoxybenzoin could be condensed with **3** under base-catalyzed (KOH in dimethylsulfoxide) or acid-catalyzed reaction conditions.[71] Application of these condensations to 4,6-diaminoisophthaldehyde **1** leads to the 1,8-anthrazoline system (Scheme 8). Thus **1** and acetophenone gave 2,7-diphenyl-1,8-anthrazoline **61** in high yield, whereas its condensation with phenylacetaldehyde gave the 3,6-diphenyl derivative **60** in 30% yield.[83] The low yield in the last reaction is due to the pronounced self-condensation tendency of phenylacetaldehyde. Polymerization reactions of **1** with diketones, such as 2,6-diacetylpyridine, gave poly(anthrazolines) **62** of low molecular weight.[71,83]

Condensation reactions with aliphatic ketones may be exemplified by the synthesis of labeled 2-methylquinoline **64** in nearly quantitative yield from **3** and acetone[84] (Scheme 9). This reaction is one of very few Friedländer condensations that have been studied in detail. It was found that reaction took place above pH 11 with an optimum rate at pH 13.[85] At pH 7–11 no reaction was observed; at lower pH (3–5) trimerization of **3** occurred exclusively. Significantly, no intermediate condensation

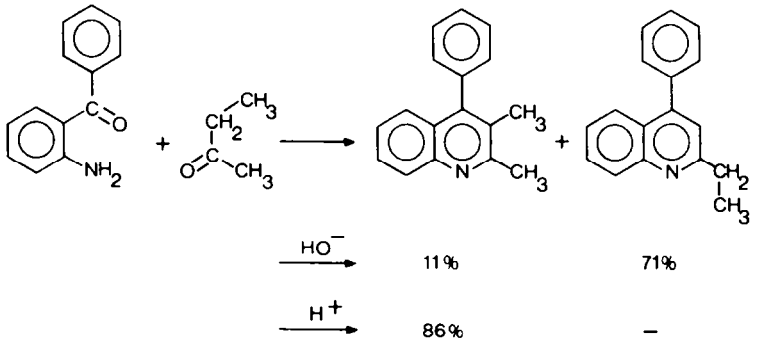


Scheme 8.



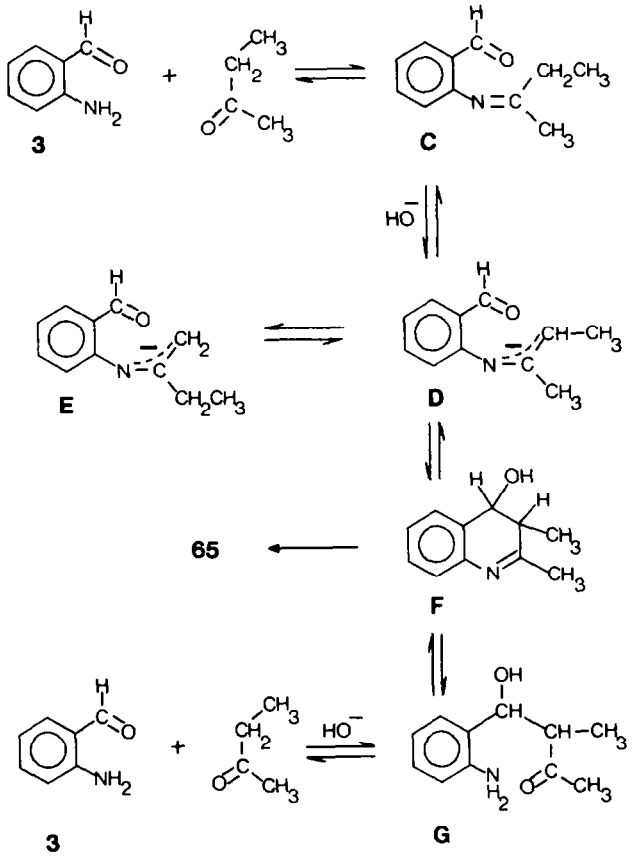
Scheme 9.

products were isolated, and this appears to be a general feature of nearly all Friedländer reactions with *o*-aminobenzaldehydes. Condensation of **3** with diacetyl gave diquinoline **67** in 50% yield.[82] Base-catalyzed condensations with unsymmetrical aliphatic ketones may in principle result in two different products, depending on which α-carbon is involved in bond formation. For linear ketones only one direction of ring closure was observed, although it is conceivable that small amounts of the isomeric products were also formed but remained undetected in the reaction mixture. Thus base-catalyzed condensation of **3** and 2-heptanone resulted in the formation of 2-methyl-3-butylquinoline **63**;[85] condensations with methyl ethyl ketone and acetonyl acetone gave 2,3-dimethylquinoline **65** and diquinoline **66**, respectively.[79] The absence of the isomeric product in the former, i.e. 2-ethylquinoline, was confirmed by NMR spectroscopy of the reaction product.[62] These examples clearly document bond formation with the α-methylene carbon in base-catalyzed Friedländer condensations with *o*-aminoaldehydes. In the closely related condensation of *o*-aminobenzophenone and methyl ethyl ketone, on the other hand, ring closure with the α-methyl group becomes the predominant reaction pathway.[57] In the acid-catalyzed annelation of this *o*-aminoketone bond formation occurred almost exclusively with the α-methylene carbon. These findings are illustrated below for comparison with the reaction of *o*-aminobenzaldehyde (eqn 18). Condensation reactions with α,β-unsaturated ketones have received very little attention. The base-catalyzed condensation of **3** and mesityloxide[86] with formation of 2-isobutenylquinoline **68** (40%) and the acid-catalyzed condensation of *o*-aminobenzaldehyde ethylene acetal **26** with 3-phenylcyclopent-2-enone[72] leading to 2-phenyl-3-*H*-cyclopenta[*b*]quinoline (77–90%) **69** have been reported. The limited information available on Friedländer condensations of ring substituted *o*-aminobenzaldehydes does not permit an evaluation of the general applicability of their annelation reactions with simple aliphatic and aromatic ketones. It has been reported that 2-aminovanillin and 6-amino-*o*-vanillin derivatives require the presence of more activated carbonyl groups for ring formation.[4,5] A successful quinoline synthesis with 6-amino-*o*-vanillin benzenesulfonate and 2-acetylpyridine has been reported recently as part of a synthetic approach to the structure of streptonigrin.[87]

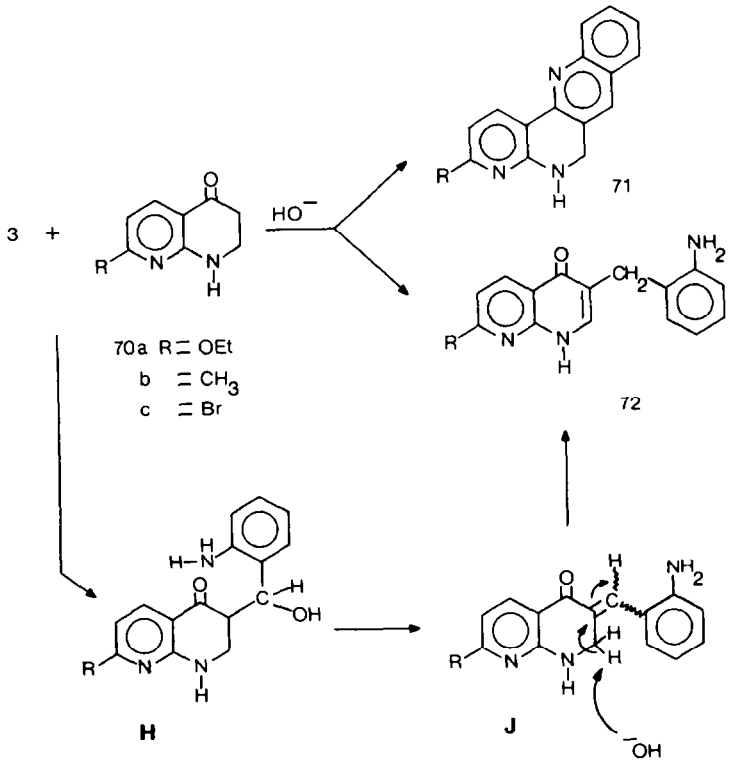


eqn 18

Formation of the quinoline ring system from *o*-aminobenzaldehyde and ketones is clearly the result of a combined Schiff base formation and aldol condensation, although the chronological order of these two processes is not known, and no conclusive experimental data in support of a specific sequence of elementary steps are available. The ready reversibility of both the aldol condensation and Schiff base formation needs to be borne in mind for a detailed understanding of the Friedländer condensation and the contrasting behavior of *o*-aminoaldehydes and *o*-aminoketones. According to one point of view, a reversible condensation reaction between the amino group and the carbonyl group of the ketone precedes carbon–carbon bond formation.[57,58] This leads to the Schiff base **C** as illustrated in Scheme 10 for the base-catalyzed condensation of **3** and methyl ethyl ketone. Subsequent proton abstraction would then produce iminate anions **D** and **E**, with the former the more stable species. Ring closure of **D** produces the β-hydroxy-Schiff base **F**, which in the present case would be dehydrated faster than its competitive retro reaction to anil **C**. In the analogous reaction with *o*-aminobenzophenone, on the other hand, retro reaction of the corresponding β-hydroxyanil would be faster than its dehydration due to the greatly increased steric interaction, and the final product of this condensation would then result from anion **E**. Such a critical role of the reversibility of aldol condensations is also responsible for the observed product formation via the α-methyl group in base-catalyzed reactions of $R-CH_2-CO-CH_3$ ketones with aromatic aldehydes.[89] In an alternative



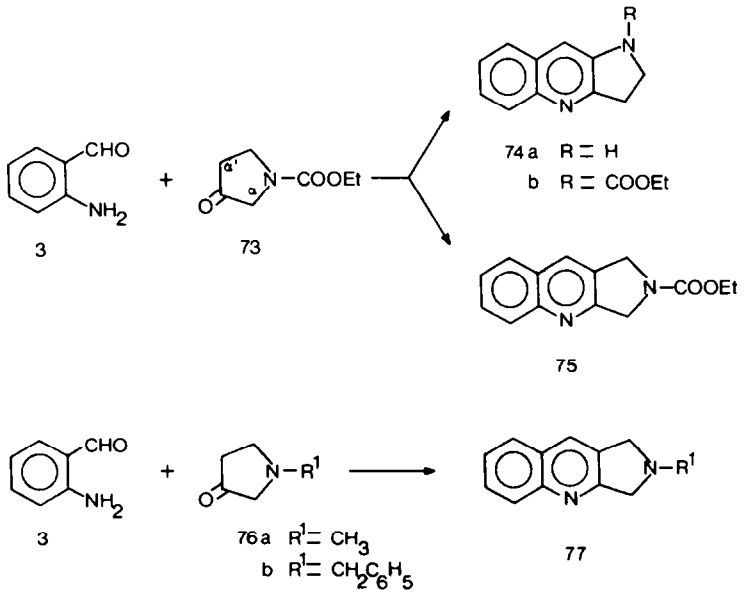
Scheme 10.



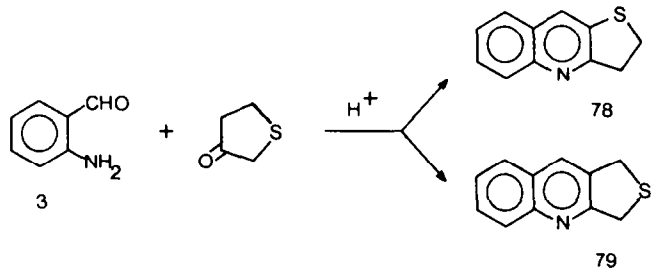
eqn 19

view of the Friedländer condensation[7,57,83] carbon-carbon bond formation via the enolate anion of the ketone would lead to β-hydroxyketone **G**, for which three competitive pathways for further transformation may be envisioned: intramolecular Schiff base formation, dehydration, and retroaldol condensation. The generally observed absence of intermediate condensation products seems to indicate that Schiff base formation is substantially faster than dehydration. Indeed, this last process would result in an α,β-unsaturated ketone, wherein the amino and carbonyl group would not necessarily be in the right configuration for ring closure. Of course steric effects on the retroaldol condensation would be identical to those in the previously discussed alternative sequence of reaction steps. The existence of such a delicate balance between competing dehydration of β-hydroxyketones **G** and intramolecular Schiff base formation is revealed by the condensation reactions of *o*-aminobenzaldehyde and 7-substituted-2,3-dihydro-1,8-naphthyridin-4(1*H*) one **70** (eqn 19). Base catalyzed condensation of **3** and **70a** (R=OEt) gave the expected annelation product **71a** in 34% yield together with a noncyclized product (26%), for which analysis and spectroscopic data are in agreement with its formulation as **72a**.[73] In the reaction of **70b** (R=CH_3) the uncyclized product **72b** was also obtained although in much lower yield (5%) together with **71b** (83%); no **72c** was reported for the condensation of **3** and **70c** (R=Br).[73] Acid-catalyzed condensations on the other hand gave the fully ring closed products **71a–c** exclusively. Formation of **72** in the base-catalyzed Friedländer condensation of **70** can only be interpreted in terms of an initial aldol condensation with formation of β-hydroxyketone **H** (eqn 19). Dehydration would lead to the α,β-unsaturated ketone **J**, which is removed from the equilibria with **H** and **70** by an irreversible base-catalyzed allylic rearrangement with formation of **72**. Such double bond transpositions are well documented in analogous systems.[90] The presence of the naphthyridone moiety in **72** prevents ring closure with the amino group, even when treated with acid.[73] The yield dependency of **72** on the substituent R seems to reflect its influence on the electrophilic character of the carbonyl group in **70**, which in turn determines the outcome of the competition at the β-hydroxyketone stage.

A direct comparison of the base-catalyzed and acid-catalyzed condensation of *o*-aminobenzaldehydes with unsymmetrical aliphatic ketones is found in the reaction of **3** with ethyl-3-oxopyrrolidine-1-carboxylate **73**[64] (eqn 20). In the base-catalyzed condensation the two possible modes of ring closure were observed with 1-*H*-pyrrolo[3,2-*b*]quinoline **74a** as the major product (81%) and 1-*H*-pyrrolo[3,4-*b*]quinoline **75** as the minor product (19%). The fact that the *N*-ethoxycarbonyl group was hydrolyzed in the formation of **74** and not of **75** does not alter the stereochemical outcome of this condensation reaction. The predominant formation of **74a** is clearly the result of an increased stability of the enolate or iminate derived from the α-carbon. In the reaction of **3** with *N*-methyl-[59] and *N*-benzyl-3-pyrrolidone[91] (**76a–76b**) on the other hand, only one product **77a–77b** was isolated in 51 and 88% respectively, although it is conceivable that the other isomer was present in small amounts. The reaction of **3** and **73** carried out in acetic acid containing sulfuric acid

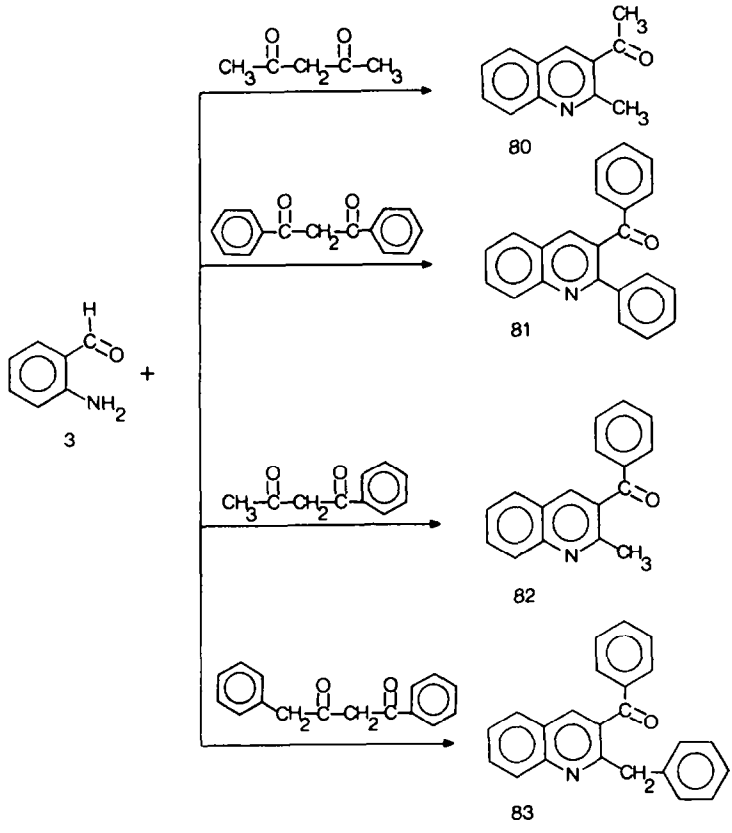


eqn 20



eqn 21

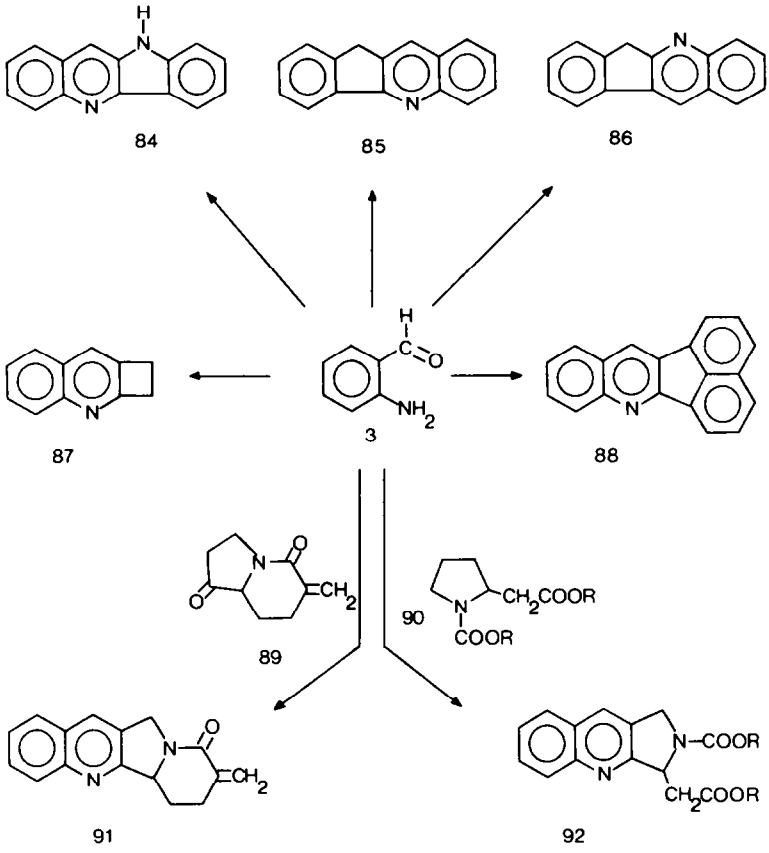
gave a mixture of **74b** (36%) and **75** (29%), indicative of the nearly equal stability of the two possible enols derived from **73**. A neat mixture of **3** and **73** heated for a short time at 190° in the presence of toluene-*p*-sulfonic acid, on the other hand, gave **75** as the major product (88%) and **74b** in 12% yield.[64] The comparable acid-catalyzed condensation of **3** with 4,5-dihydrothiophene-3-one in acetic acid gave a 2:1 mixture of the isomeric dihydrothienoquinolines **78** and **79**,[68] reflecting a greater difference in stability of enols derived from the dihydrothiophene as compared to those derived from **73**. Base-catalyzed condensations were not reported (eqn 21).



Scheme 11.

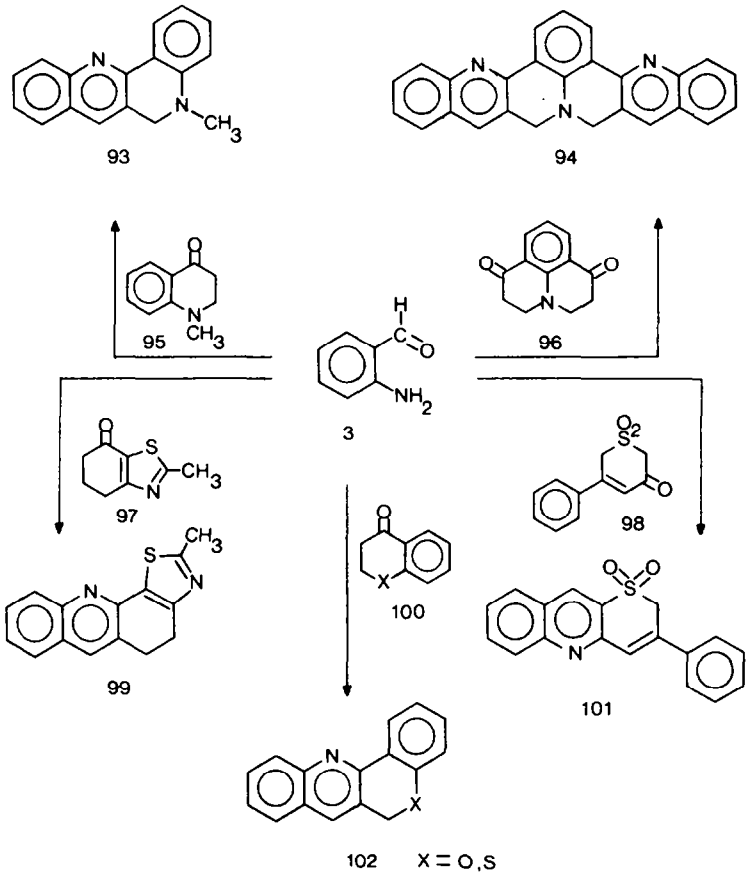
Condensation reactions of β-diketones and *o*-aminobenzaldehydes (Scheme 11) are greatly facilitated by the presence of a doubly activated α-methylene group, and as expected only one direction of annelation is observed as illustrated for the reaction of **3** with acetylacetone with formation of 2-methyl-3-acetylquinoline **80** in nearly quantitative yield.[79,92] Condensation with 2-aminoveratraldehyde, which is unreactive in the presence of monoketones, gave 2-methyl-3-acetyl-7,8-dimethoxyquinoline in 60% yield.[4] It is noteworthy that *o*-aminobenzophenone reacts in a similar way[93] and not at the methyl group as reported earlier.[94] Base-catalyzed condensations of **3** with dibenzoylmethane did not result in the formation of 2-phenyl-3-benzoylquinoline **81** but gave 2-phenylquinoline via condensation of **3** with acetophenone formed by base induced degradation of the starting β-diketone. Thermal condensation however, gave **81** in 80% yield.[95] In condensation reactions with unsymmetrical β-diketones Schiff base formation with the more reactive carbonyl

group is observed exclusively. Thus, **3** and benzoylacetone gave 2-methyl-3-benzoylquinoline **82** in 80% yield.[95] 2-Benzyl-3-benzolyquinoline **83**, a key intermediate for the synthesis of pyrolo[3,4-*b*]- and thieno[3,4-*b*]quinolines was obtained from **3** and phenylacetylacetophenone.[96] β-Ketoaldehydes do not form quinoline derivatives when reacted with *o*-aminobenzaldehyde.[79]



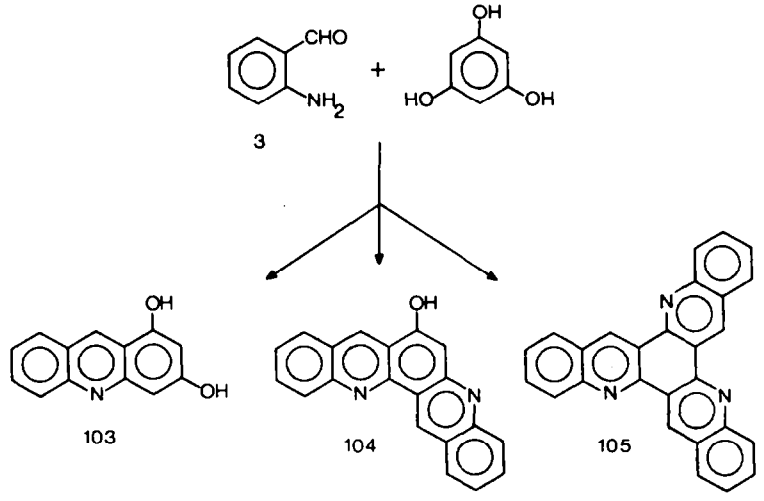
Scheme 12.

Reactions of *o*-aminoaldehydes with cyclic ketones are especially valuable for the construction of polycondensed heterocyclic systems. The direction of annelation and the position of the heteroatom(s) are in general uniquely defined by the participating functional groups (the rare examples of cyclic ketones with two nearly identical α-methylene groups were discussed earlier). The availability and structural variety of cyclic ketones provide easy and direct access to a large number of fused heterocyclic systems for which in many cases alternate annelation methods are not readily available. Furthermore, the mild reaction conditions employed in the Friedländer condensations (see above) permit the unaltered transposition of functional groups from the starting ketone into the annelated heterocyclic ring. The scope of this heteroannelation is illustrated with a few selected examples in Schemes 12 and 13. Base-catalyzed condensation of **3** with cyclobutanone gave the interesting strained heterocycle **87** in 60% yield, also available via acid-catalyzed condensation of the components although in much lower yield.[62] Acenaphtho[1,2-*b*]quinoline **88** was obtained from **3** and acenaphthenone in 70% yield.[97] Condensations with 1-indanone[60] and 2-indanone[61] gave indenoquinolines **85** and **86**, respectively. Condensation reactions of *o*-aminobenzaldehyde with heterocyclic 5-membered ring ketones have been employed extensively in synthetic approaches to the interesting alkaloid camptothecin.[99] Base-catalyzed condensation of **90** and **3** gave **92** in moderate yield,[99,100] which is better prepared[63] by an acid-catalyzed modification of the Friedländer condensation (see below). The compatibility of these heteroannelations with the presence of sensitive functional groups may be illustrated by the reaction of the complex ketone **89** and *o*-aminobenzaldehyde with formation of **91** in 33% yield via a base-catalyzed reaction and in 76% yield via the acid-catalyzed condensation of the anil-protected **3**[70] (see below). Condensations with indoxyl[101] or indoxyl-2-carboxylic acid[102] gave carboline **84**. Numerous 6-membered ring ketones

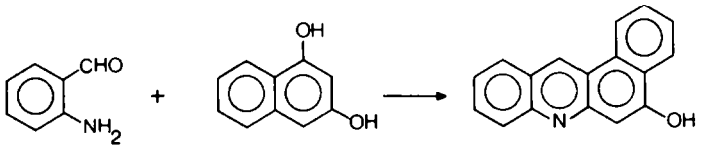


Scheme 13.

have been converted into fused systems via their annelation with *o*-aminoaldehydes. Base-catalyzed condensation of **3** and **97** gave thiazolo[4,5-*c*]acridine **99** in 75% yield;[103] thiopyranone dioxide **98** was converted into the thiopyrano[3,2-*b*]quinoline-1,1-dioxide **101** in a melt reaction with **3** in 70% yield.[104] A large number of substituted piperidones[59] and pyrrolidones[59,91] have been condensed with *o*-aminobenzaldehyde in base-catalyzed reactions. The interesting dihydroquinolino[4,3-*b*]quinoline **93** and the similar heptacyclic system **94** were obtained in high yield from quinolone **95** and 1,6-dioxojulolidine **96**, respectively.[105] 4-Chromanones **100** (X = 0) could be condensed successfully to form **102** in the reaction with the "hydrochloride salt" of *o*-aminobenzaldehyde, obtained by treating an ether solution of **3** with HCl gas.[66,67] The structure of this salt, which most



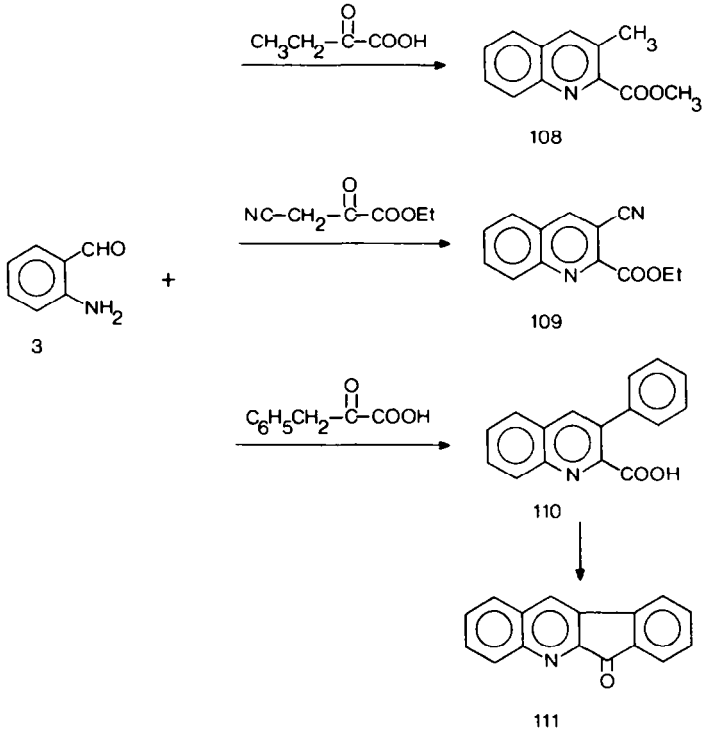
eqn 22



3 106 107 eqn 23

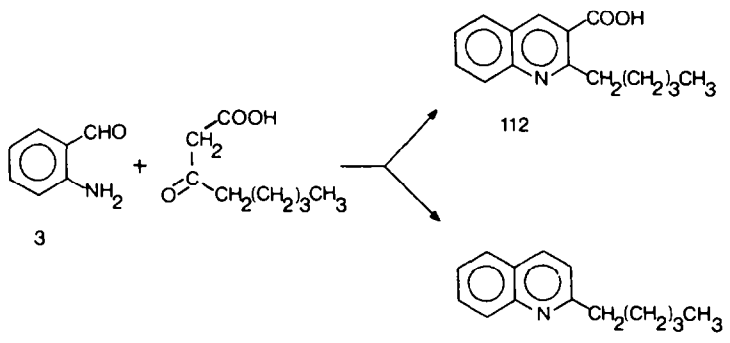
likely is a self-condensation product of *o*-aminobenzaldehyde, remains to be established. Reactions of cyclic polyketones may be illustrated by the reaction of **3** with phloroglucinol which, depending on the ratio of the reactants, gave **103**, **104**,[101,106] or the heptacyclic **105**[106] (eqn 22). Base-catalyzed condensations of **3** and naphthalene-1,3-diol **106** gave benz[*a*]acridine-5-ol **107** (75%) and not benzo[*c*]acridin-6-ol[107] as would be expected from the formation of **83** via the condensation of **3** and phenylacetylacetophenone (eqn 23).

The incorporation of functional groups in the annelating ketone gives added versatility to the Friedländer synthesis. Such groups are generally transferred unaltered into the newly created heterocycle and may often be used for additional ring closing reactions. Condensation reactions of *o*-aminoaldehydes and α-ketoacids (eqn 24) provide nonoxidative entry into 3-substituted quinoline-2-carboxylic acids as illustrated for the base-catalyzed condensation of **3** with 2-oxobutyric acid[108] and the acid-catalyzed condensation with 3-cyano-3-sodiopyruvate[65,69] with formation of 2-carbomethoxy-3-methylquinoline **108** (87%) and 2-carboethoxy-3-cyanoquinoline **109** (37%), respectively. Reaction of **3** with phenylpyruvic acid gave 3-phenylquinoline-2-carboxylic acid **110** (90%), which was readily converted into the fused heterocycle **111**.[109]



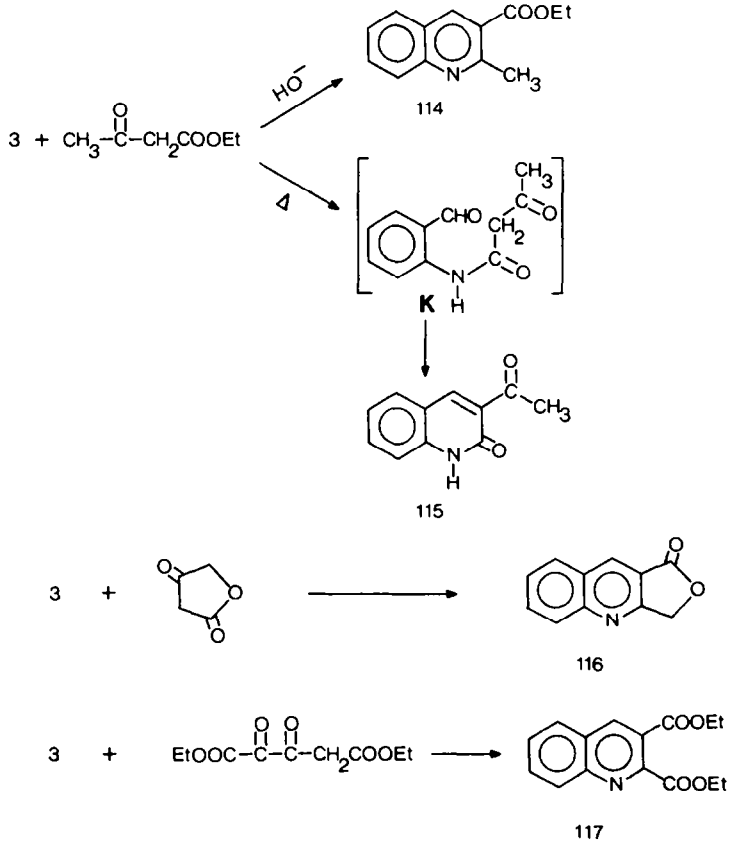
3 108 109 110 111 eqn 24

The analogous condensation reactions with β-ketoacids may be expected to give the isomeric 2-substituted quinoline-3-carboxylic acids based on the preferred ring closure with the more activated α-methylene carbon. It was found, however, that the outcome of these condensations was dependent on the pH of the reaction medium. At pH 13 the anticipated quinoline-3-carboxylic acids were obtained in nearly quantitative yield; condensations conducted between pH 5 and 11 were accompanied by decarboxylation and gave 2-substituted quinolines in good yield. At lower pH no condensation products could be obtained and only trimerization of the *o*-aminoaldehyde took place. This is illustrated for the reaction of **3** with 3-oxooctanoic acid with formation of 2-pentylquinoline-3-carboxylic acid **112** at pH 13 and 2-pentylquinoline **113** in the intermediate pH range[85] (eqn 25). It



eqn 25

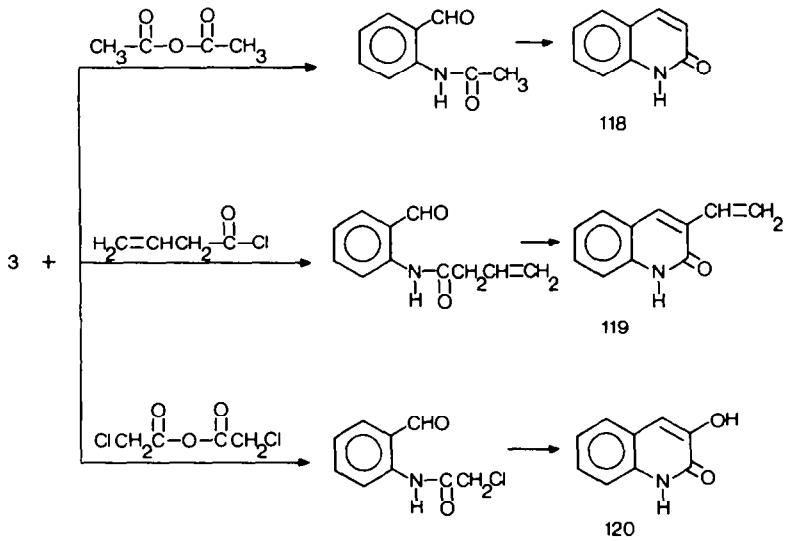
should be noted that the latter is not accessible *via* condensations of **3** with ketones (see above). Aldol condensations accompanied by decarboxylation have also been observed in condensations of β-ketoacids with simple aromatic aldehydes.[110] Although the detailed sequence of events in such condensation/decarboxylation reactions is not known, it appears that in the present case some preliminary condensation reaction must precede decarboxylation in order to account for the exclusive formation of the monosubstituted quinoline **113**. Such a decarboxylative pathway is not possible in condensation reactions with β-ketoesters, and their base-catalyzed reactions lead therefore to 2-substituted quinoline-3-carboxylic acid esters exclusively. Thus, **3** and ethyl acetoacetate gave **114**[76] and the cyclic β-ketoester, tetronic acid, gave quinoline lactone **116** in 73% yield.[88] Quinoline-2,3-dicarboxylate **117** is accessible via the reaction with diethyl oxalacetate[111] (eqn 26). The presence of two different electrophilic sites in the starting β-ketoesters provides the possibility for an alternative ring closure whereby the ester group, rather than the ketone moiety, undergoes nucleophilic addition by the aromatic amine. This mode of annelation leads to 3-acyl-2-quinolones, such as **115**, and may be effected by heating a neat mixture of the reactants in the absence of catalysts.[76,112] The first elementary step of this ring closure is undoubtedly formation of the intermediate anilide **K**, which



eqn 26

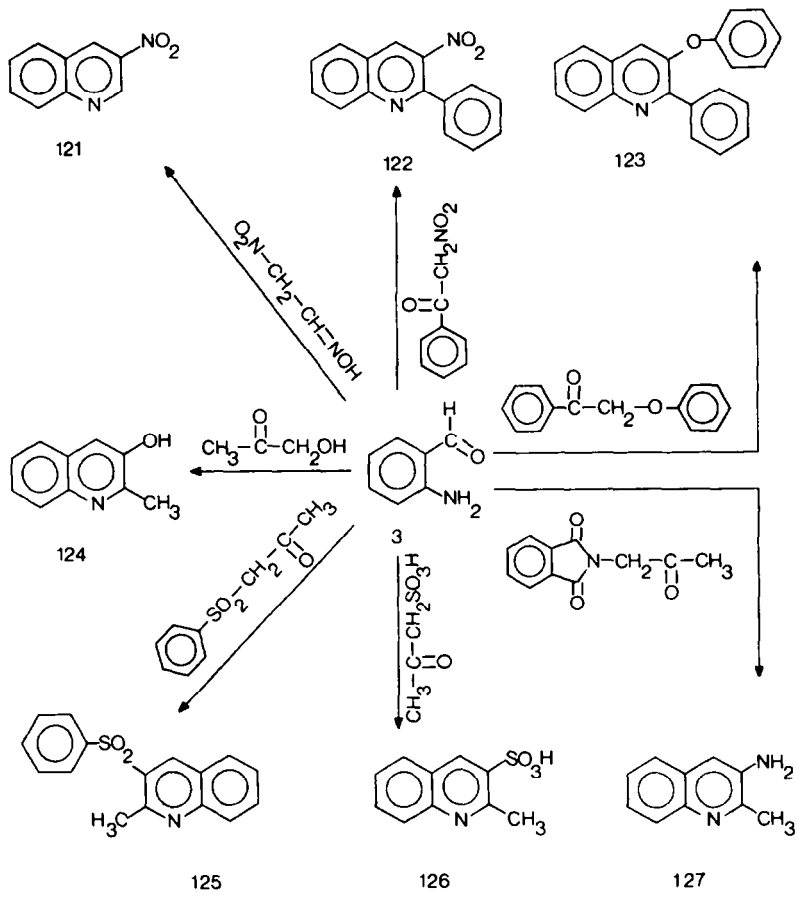
would be expected to undergo ready intramolecular aldol condensation with the activated methylene group[88] (eqn 26). Different modes of cyclization with β-ketoesters have also been reported for ring substituted *o*-aminobenzaldehydes, such as 2-amino-3-methoxy-[113] and 2-amino-5-methoxybenzaldehyde.[114]

Reactions of *o*-aminoaldehydes with acid chlorides or anhydrides lead to acylated derivatives structurally analogous to the proposed intermediate **K**. Their reactions with base follow the cyclization pathway described for the thermal condensation of *o*-aminoaldehydes and β-ketoesters and result in the formation of 2-quinolones (eqn 27). Thus, treatment of **3** with acetic anhydride/sodium acetate gave 2-(1*H*)quinolone **118**.[7] 3-Vinyl-2-quinolone **119**, a key starting material for the synthesis of the furo[2,3-*b*]quinoline system, was obtained from **3** and 3-butenoylchloride followed by treatment with ethanolic potassium hydroxide.[115,116] 3-Hydroxy-2-quinolone **120** was obtained similarly from **3** and chloroacetic anhydride.[117] These acylated derivatives may also be converted into quinazolines upon treatment with ethanolic ammonia (see above, e.g. **36** → **33**).



Condensation reactions of *o*-aminoaldehydes with ketones containing functional groups *alpha* to the carbonyl moiety follow the normal annelation pattern with concomitant introduction of the functional group in the 3-position of the quinoline ring system. Some typical examples are collected in Scheme 14. Reaction of **3** with α-nitroacetophenone in refluxing ethanol, without added catalyst, gave 3-nitro-2-phenylquinoline **122** in 50% yield.[118] 3-Nitroquinoline **121** may be obtained in 48% yield from **3** and methazonic acid.[119] Direct introduction of an amino group in the β-position of the quinoline ring system was accomplished *via* condensation reaction with *N*-acetonylphthalimide to give **127** in good yield.[120,121] Phenylphenacyl ether and **3** gave 3-phenoxy-2-phenylquinoline **123** in 84% yield;[122] the corresponding thioether did not result in the formation of the thio analog of **123**.[123] Condensation of **3** and hydroxyacetone gave the highly fluorescent 3-hydroxy-2-methylquinoline **124**.[124] 2-Methylquinoline-3-sulfonic acid **126**[125] and quinoline sulfone **125**[126] were obtained from acetonesulfonic acid and benzenesulfonacetone, respectively. The related condensation with benzenesulfonacetophenone could only be carried out at high temperature.

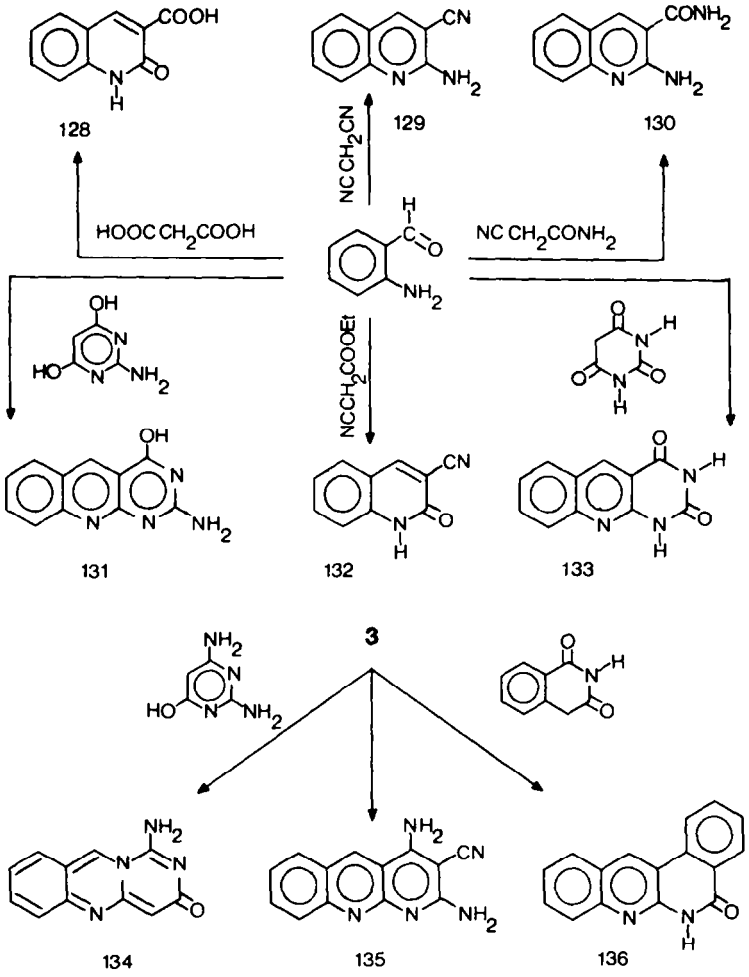
Malonic acid derivatives can be readily condensed with *o*-aminobenzaldehydes with formation of functionalized quinolines, which in turn are attractive starting materials for further ring annelations (Scheme 15). With malononitrile and cyanoacetamide, cyclization takes place via intramolecular addition of the amino group on the nitrile function to give 2-amino-3-cyanoquinoline **129** and 2-aminoquinoline-3-carboxamide **130** in 75% yield.[128] With ethyl cyanoacetate, on the other hand, ring closure involved the ester group as evidenced by the formation of 3-cyano-2(1*H*)-quinolone **132**.[129] Malonic acid gave 2-(1*H*)quinolone-3-carboxylic acid **128** in a melt reaction with **3**.[76] Condensation of **3** with barbituric acid provides easy access to the pyrimido [4,5-*b*]quinoline **133**.[130] Extension of this annelation to 2-amino-4,6-dihydroxypyrimidine gave **131** in 70% yield.[131] 2-Dimethylamino-4,6-dihydroxy- and 4-dimethylamino-2,6-dihydroxypyrimidine did not form condensation products with *o*-aminobenzaldehyde. Their failure to form pyrimidoquinolines implies that



Scheme 14.

triketo tautomerism in barbituric acid derivatives is an essential requirement for condensation reactions with *o*-aminoaldehydes.[131] Condensation reaction of **3** with 2,4-diamino-6-hydroxypyrimidine did not result in the formation of the pyrimido[4,5-*b*]quinoline ring system but gave a condensation product formulated as **134**.[131] Its formation was rationalized as the result of nucleophilic addition of the 3-nitrogen ring atom to the aldehyde followed by loss of ammonia. 4,6-Diamino-2-hydroxy- and 2,4,6-triaminopyrimidine also failed to form condensation products with *o*-aminobenzaldehyde. Annelation reaction with the related homophthalimide gave the tetracyclic ring system **136**.[132] The benzo[*b*]1,8-naphthyridine **135** is available via condensation of **3** with 2-amino-1,1,3-tricyanopropene (dimeric malononitrile).[133]

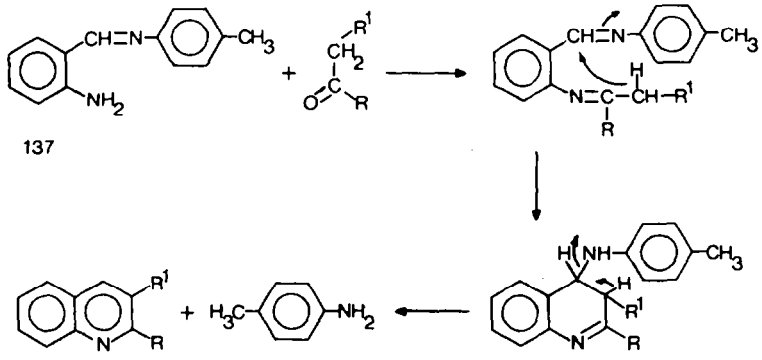
A useful modification of the Friedländer quinoline synthesis employs anils of *o*-aminobenzaldehydes, generally *o*-aminobenzaltoluidine **137** and is known as the Borsche quinoline synthesis.[101,134,135] The anil **137** is a stable compound which does not form self-condensation products upon standing. It is available from *o*-nitrobenzaldehyde via condensation with *p*-toluidine followed by reduction of the nitro group with sodium sulfide. This modification is especially attractive for ring-substituted derivatives where the *o*-aminoaldehyde, required for the Friedländer condensation, is synthesized by hydrolysis of the corresponding anil (e.g. 6-aminopiperonal and 6-amino veratraldehyde).[3,10] The Borsche synthesis has been applied to a large number of aliphatic and aromatic ketones, ketoesters, and malonic acid dervatives. In most cases the results are comparable with the Friedländer condensations discussed earlier, except for condensations with α-ketoacids, which failed to form quinolines in their reaction with anil **137**. Borsche condensations are generally carried out with base catalysis; a few acid-catalyzed reactions have been reported as part of synthetic efforts leading to the camptothecin system (see above).[63,70] The mechanism of the Borsche synthesis most likely involves initial Schiff base formation followed by nucleophilic addition to the C=N bond and elimination of *p*-toluidine (eqn 28). The increased reactivity of the anil derived from 6-aminoveratraldehyde is consistent with this sequence of events.



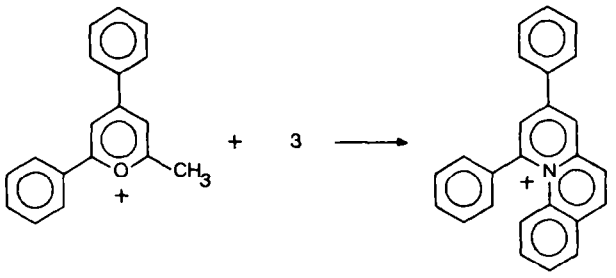
Scheme 15.

Many quinoline derivatives accessible via the Friedländer and Borsche condensation, may also be prepared by the Pfitzinger reaction with isatin or isatoic acid.[56] This synthetic method requires a final decarboxylation step, which is often difficult and incompatible with the presence of sensitive groups. A comparison with annelations of *o*-aminoaldehydes is beyond the scope of this review.

As pointed out earlier, annelation of *o*-aminoaldehydes and carbonyl compounds results from the presence of matching pairs of nucleophilic-electrophilic sites in the annelating reactants. Such dual capability may also be found in other functional systems and should provide therefore additional opportunities for heteroannelations with *o*-aminoaldehydes. Pyrylium salts with a methylene group in the 2- or 6-position of the nucleus possess the required reactivity features for annelation reactions with *o*-aminobenzaldehyde. Thus, reaction of 3 with 2-methyl-4,6-diphenylpyrylium salts resulted in



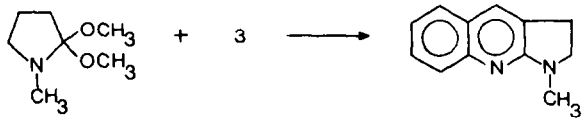
eqn 28



138

eqn 29

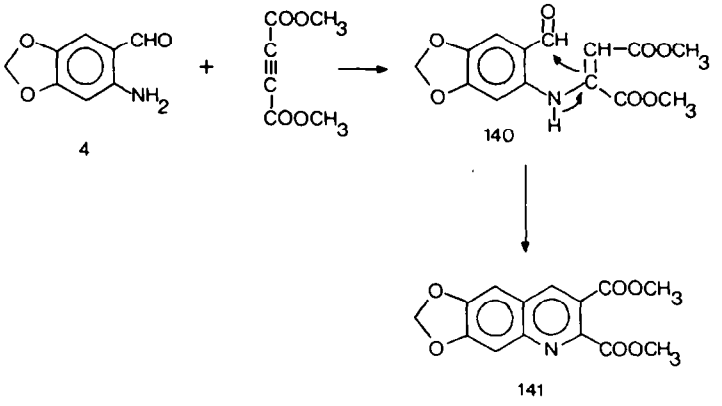
the formation of the benzo[*c*]quinolizidinium ion **138** in approximately 70% yield[136] (eqn 29). The first step in this transformation most likely involves attack of the amino group on the pyrylium nucleus resulting in an intermediate pyridinium salt, which would undergo ring closure via condensation of the aldehyde and the activated methyl group. Adjacent centers of opposite reactivity are also present in lactam acetals, which are in equilibrium with iminium lactim ether and enamine forms.



139

eqn 30

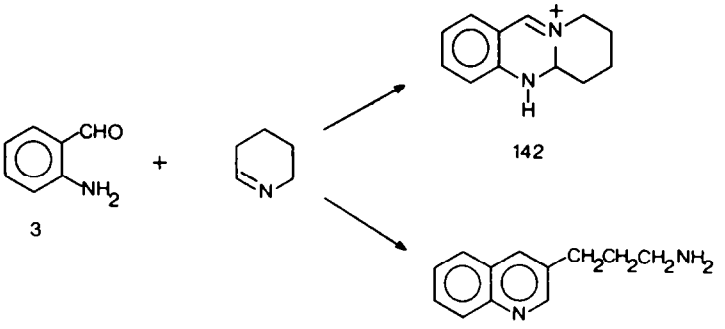
Treatment of 1-methyl-2,2-dimethoxypyrrolidine gave **139** in moderate yield after treatment with sulfuric acid[137] (eqn 30). Lactams are unreactive towards *o*-aminobenzaldehyde.[59] Addition reaction of dimethyl acetylenedicarboxylate and 6-aminopiperonal **4** was reported to give quinoline-2,3-dicarboxylate **141** in 50% yield[138] (eqn 31). This reaction involves addition of the amino group to the triple bond with formation of the intermediate aldehyde **140**, which could be isolated (no experimental details available). Dibenzoylacetylene and **3** gave 2,3-dibenzoylquinoline in low yield[96] via a similar pathway. It appears that electron donating groups in the aromatic ring facilitate this type of annelation reaction, which is consistent with the proposed mechanism.



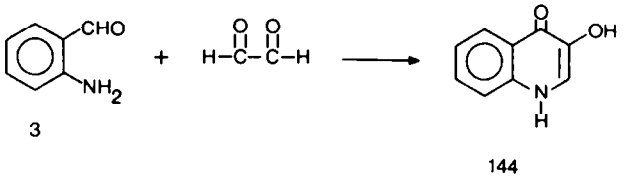
4 140 141

eqn 31

Adjacent electrophilic and nucleophilic sites are also present in the C=N linkage. Reaction of **3** with Δ^1-piperideine (introduced as the trimer) in aqueous or alcoholic medium at room temperature gave the deep yellow quinazolinium ion **142** in quantitative yield (isolated as the picrate)[139] (eqn 32). A similar condensation reaction was observed with Δ^1-pyrroline.[140] The intense, yellow color of these quinazolinium ions has been used for the determination of the C=N-linkage in the structural elucidation of several alkaloids.[141–144] Condensation of **3** with Δ^1-piperideine at 100° did not result in the formation of **142** but gave 3-(3'aminopropyl-)quinoline **143** in good yield.[139] It appears likely that under these conditions carbon–carbon bond formation takes place *via* the tautomeric enamine form, which is unreactive at room temperature.[143] Reaction of **3** with glyoxal bisulfite in the presence of



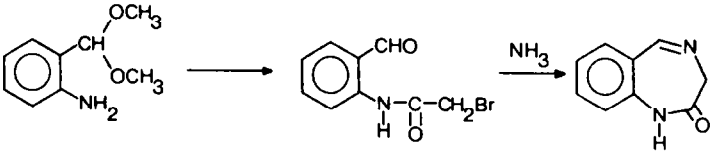
eqn 32



eqn 33

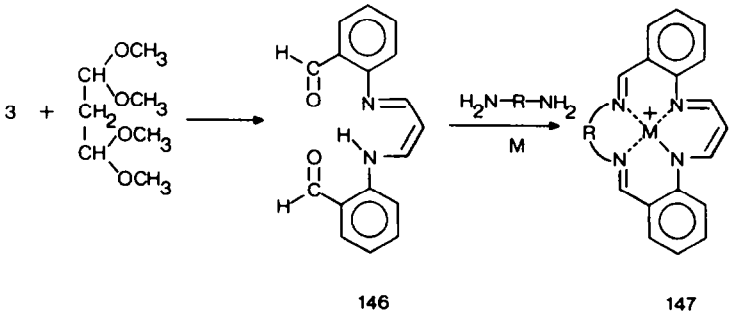
potassium cyanide gave 3-hydroxy-4(1*H*)quinolone **144** in 64% yield[145] (eqn 33). The formation of **144** is the result of Schiff base formation and acyloin condensation; their chronological order is however unknown.

Heteroannelation reactions with *o*-aminobenzaldehyde to give fused ring systems containing a seven membered ring have received very little attention. In one example, 1,3-dihydro-2*H*-1,4-benzodiazepin-2-one **145** was obtained in 35% overall yield by the sequence outlined in (eqn 34).[51]



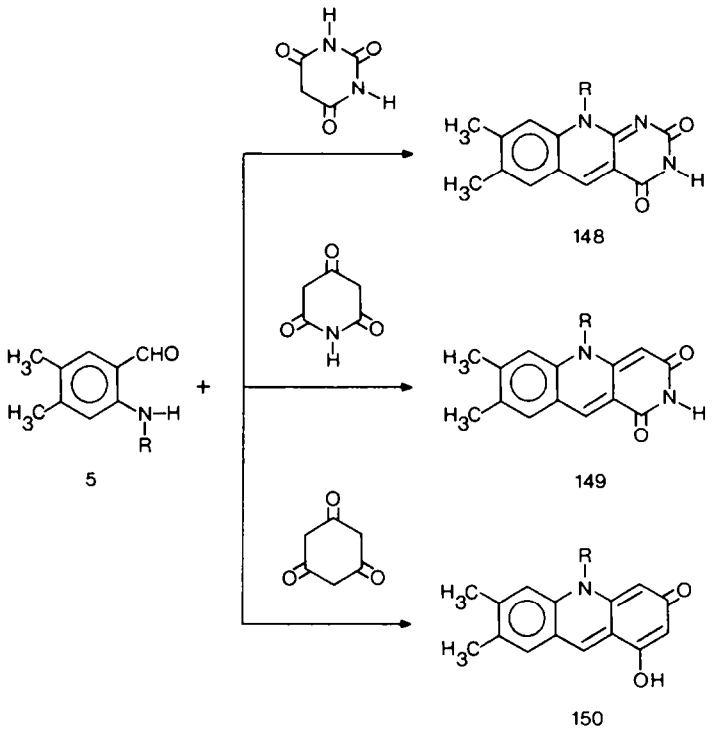
eqn 34

Metal template reactions on *o*-aminobenzaldehyde derivatives have been investigated as a source of novel synthetic macrocylic ligands.[146] This is illustrated for the reaction of **3** with 1,1,3,3-tetramethoxypropane, which gave aminoaldehyde **146** (obtained as a 1:1 mixture of *Z*, *E* and *E*, *E* isomers). Reaction of **146** with a series of diamines in the presence of metal salts resulted in the formation of macrocyclic complexes **147**[146] (eqn 35).



eqn 35

Few condensation reactions of *N*-substituted *o*-aminobenzaldehydes have been reported. A notable example is the synthesis of 5-deazariboflavine **148**, a valuable tool in flavine chemistry, via the condensation reaction of 2-*N*-ribitylamino-4,5-dimethylbenzaldehyde **5** with barbituric acid.[14] 1,5-Dideaza- (**149**) and 1,3,5-trideazariboflavine **150** were similarly obtained from **5** and 2,4,6-trioxopiperidine and phloroglucinol, respectively[147] (eqn 36).



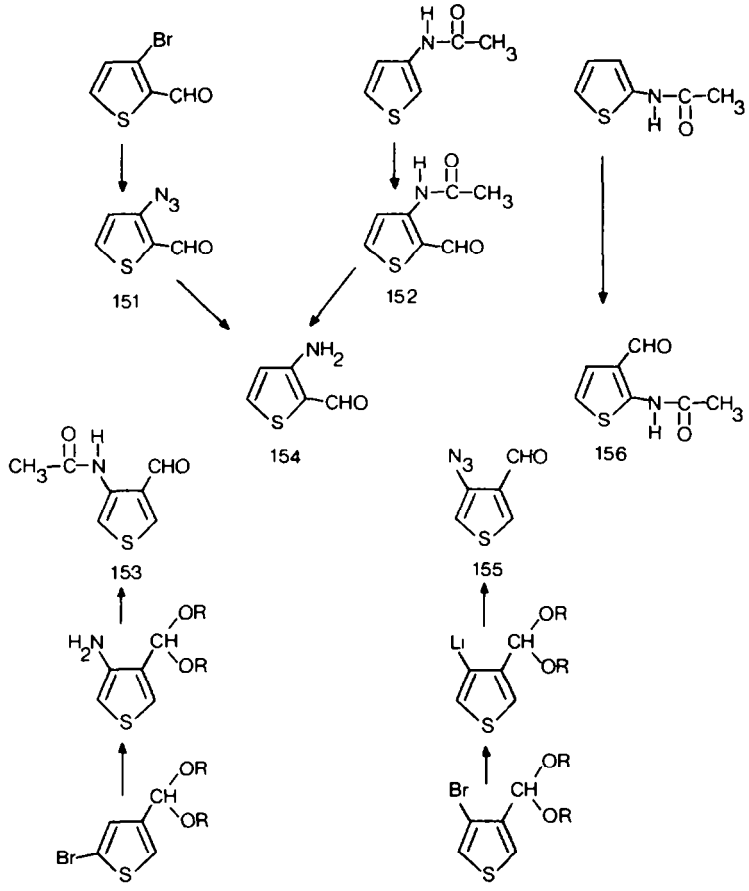
eqn 36

HETEROANNELATIONS WITH HETEROCYCLIC AMINOALDEHYDES

Heterocyclic aminoaldehydes are generally accessible from aminocarboxylic acid precursors by a number of different reductive methods. The aldehyde function is thus elaborated in the presence of the amino group, in contrast with the standard method employed in the carbocyclic series wherein the reverse order of introduction is followed. This reversal simply reflects the inaccessibility of suitable heterocyclic nitromethyl precursors. The stability of most heterocyclic aminoaldehydes in acid medium permits their elaboration via synthetic methods that were not applicable to their acid-sensitive carbocyclic counterparts. Catalytic reduction of aminonitriles, conducted in acid medium to hydrolyze the intermediate aminoimines, is a valuable synthetic method for heterocyclic aminoaldehydes, since the starting aminonitriles are readily accessible.[1] The absence of acid catalyzed self-condensation also permits the direct *C*-formylation of π-excessive heterocycles possessing an appropriately located amino group. The simultaneous introduction of the amino and aldehyde functionalities in *N*-heterocyclic systems via Friedländer condensation of 4-aminopyrimidine-5-carboxaldehyde followed by hydrolytic cleavage of the resulting heterocycle, permits the construction of numerous heterocyclic polycyclic *o*-aminoaldehydes, for which reductive methods are not available.

Annelation reactions with heterocyclic aminoaldehydes provide synthetic entry into heterocyclic systems fused to a pyridine or pyrimidine nucleus by condensation reactions similar to those described for the carbocyclic series. A comparison of the reactivity of *o*-aminobenzaldehyde with its π-excessive and π-deficient counterparts would provide valuable insight into the detailed chronological order of reaction steps in their Friedländer reaction with ketones. The nucleophilicity of the amine and the electrophilic character of the aldehyde functionality are greatly affected by the heterocycle in which they are incorporated and it seems likely therefore that different reaction mechanisms are operative in their condensation reactions. However, quantitative comparative data on the reactivity of *o*-aminoaldehydes are not available, although different modes of annelations with polyfunctional systems have been reported.

Incorporation of the aminoaldehyde functionality in the thiophene nucleus may be accomplished either via introduction of the amino group in a substituted thiophene carboxaldehyde or via formylation of appropriate aminothiophenes (Scheme 16). The first strategy is illustrated by the nucleophilic aromatic substitution reaction of 3-bromothiophene-2-carboxaldehyde with sodium



Scheme 16.

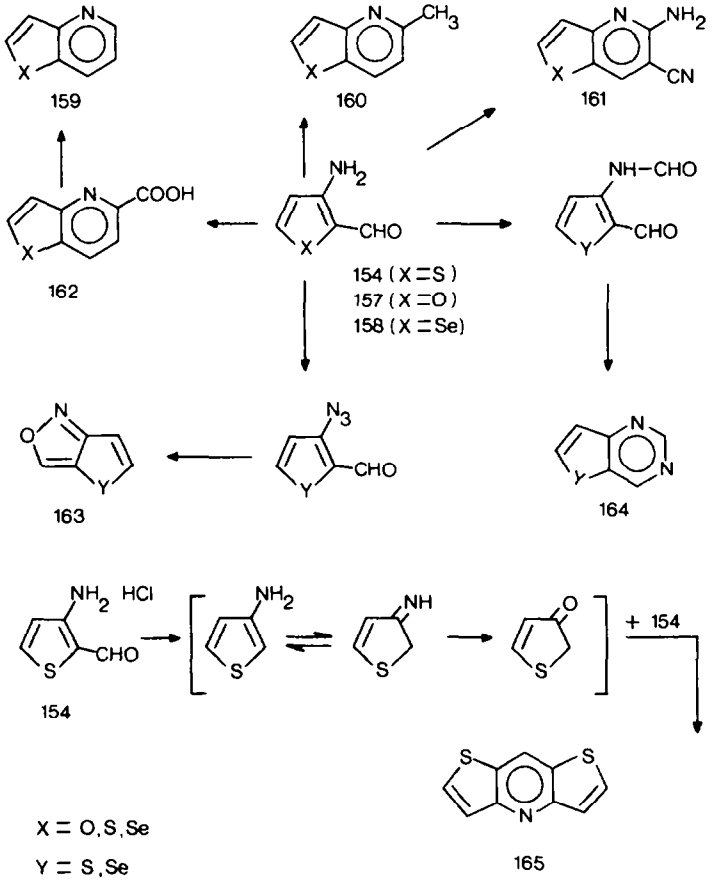
azide in dimethylsulfoxide to give 3-azidothiophene-2-carboxaldehyde **151** (48%), which was readily reduced to the aminoaldehyde **154** with hydrogen sulfide.[148] The scope of this nucleophilic substitution reaction is limited; 2- and 4-bromothiophene-3-carboxaldehydes were not converted into the corresponding azides under similar reaction conditions. 2-Nitro-3-bromothiophene-4-carboxaldehyde, on the other hand, was readily transformed in the azide. The *o*-azidothiophene-carboxaldehydes **151** and **155** are also available, in good yield, from the corresponding *o*-bromothiophene carboxaldehydes (protected as their acetals) via metalation with *n*-butyllithium in ether followed by reaction with *p*-toluenesulfonyl azide.[149] The reduction of *o*-azidoaldehyde **155** has not been reported.

Direct introduction of the aldehyde functionality in aminothiophenes is possible via Vilsmeier–Haack formylation. Thus, reaction of 3-*N*-acetylaminothiophene with phosphorus oxychloride in *N*,*N*-dimethylformamide gave 3-*N*-acetylaminothiophene-2-carboxaldehyde **152** (50%), which was deacetylated in concentrated sulfuric acid to give **154** in quantitative yield.[150] Formylation of 2-aminothiophene derivatives gave 2-*N*-acetylaminothiophene-3-carboxaldehydes[151,152] e.g. **156**. 4-*N*-Acetylaminothiophene-3-carboxaldehyde **153** is not accessible via Vilsmeier-Haack formylation of 3-*N*-acetylaminothiophene; it could be obtained in low yield from 5-bromothiophene-3-carboxaldehyde (protected as the acetal) upon treatment with potassium amide in liquid ammonia.[150]

3-Aminofurfural **157** and 3-aminoselenophene-2-carboxaldehyde **158** can be prepared via nucleophilic substitution of the corresponding *o*-bromoaldehydes and sodium azide.[148] The latter is also accessible via formylation of 3-*N*-acetylaminoselenophene.[150]

The aminoaldehydes **154**, **157**, and **158** are well characterized crystalline compounds. 3-Aminofurfural **157** is the least stable of the three and is reported to disintegrate completely upon storage for four weeks at room temperature.[148] The generation of **154** and **158** in concentrated sulfuric acid demonstrates their stability in acid medium, in marked contrast with the behavior of carbocyclic

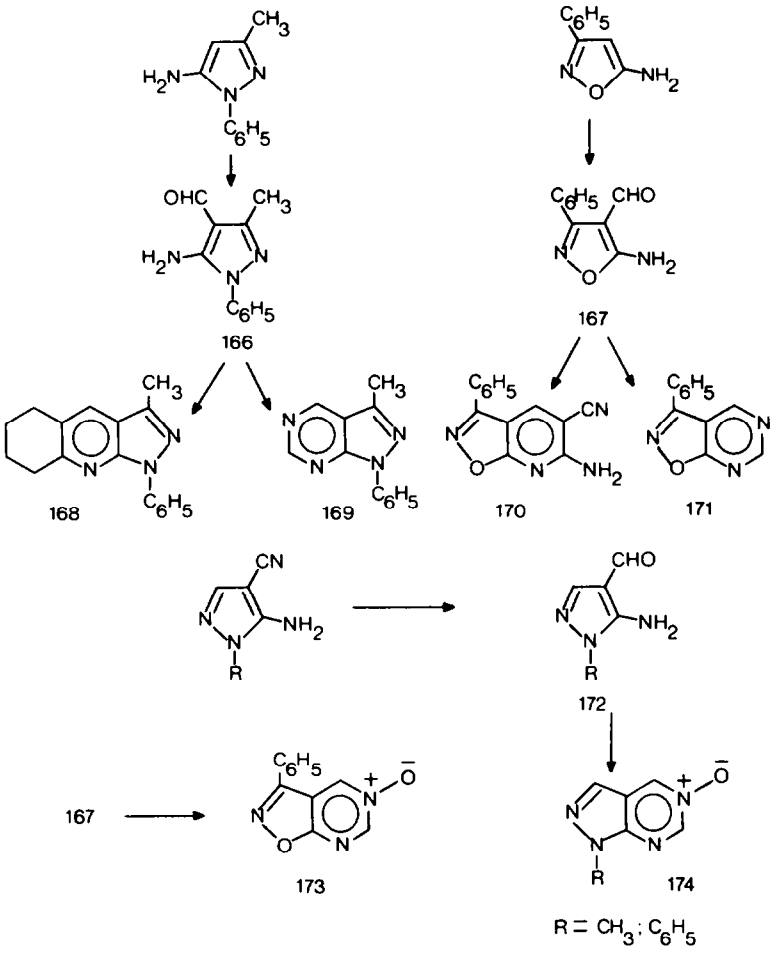
o-aminoaldehydes. These heterocyclic aminoaldehydes have not been used extensively as annelating reagents (Scheme 17). Condensation reactions of **154**, **157** and **158** with pyruvic acid gave the fused pyridinecarboxylic acids **162** in moderate yield; their decarboxylation led to the parent heterocycles: furo-, thieno- and seleno[3,2-*b*]pyridine **159**, which could not be obtained via Friedländer condensations with acetaldehyde.[153] Condensations with acetone gave the methyl substituted heterocycles **160** in high yield.[153,154] Reaction of **154** and malononitrile resulted in the formation of aminonitrile **161** in 60% yield.[154] Treatment of the hydrochloric acid salt of **154** with sodium formate in formic acid gave the interesting dithienopyridine **165** in 20% yield. This unusual condensation was rationalized as a Friedländer condensation of **154** and 3-aminothiophene, formed in the reaction medium by decarbonylation of **154**.[154] Thieno- and seleno[3,2-*d*]pyrimidines **164** were obtained in high yield from acylated **154**, **158** and ammonium formate.[150] Aminoaldehydes **154** and **158** can be diazotized normally; reaction of their diazonium salts with sodium azide resulted in the corresponding *o*-azidoaldehydes in excellent yield. Their thermal decomposition resulted in the formation of the novel heterocyclic systems: thieno- and seleno[3,2-*c*]isoxazoles **163**.[155]



Scheme 17.

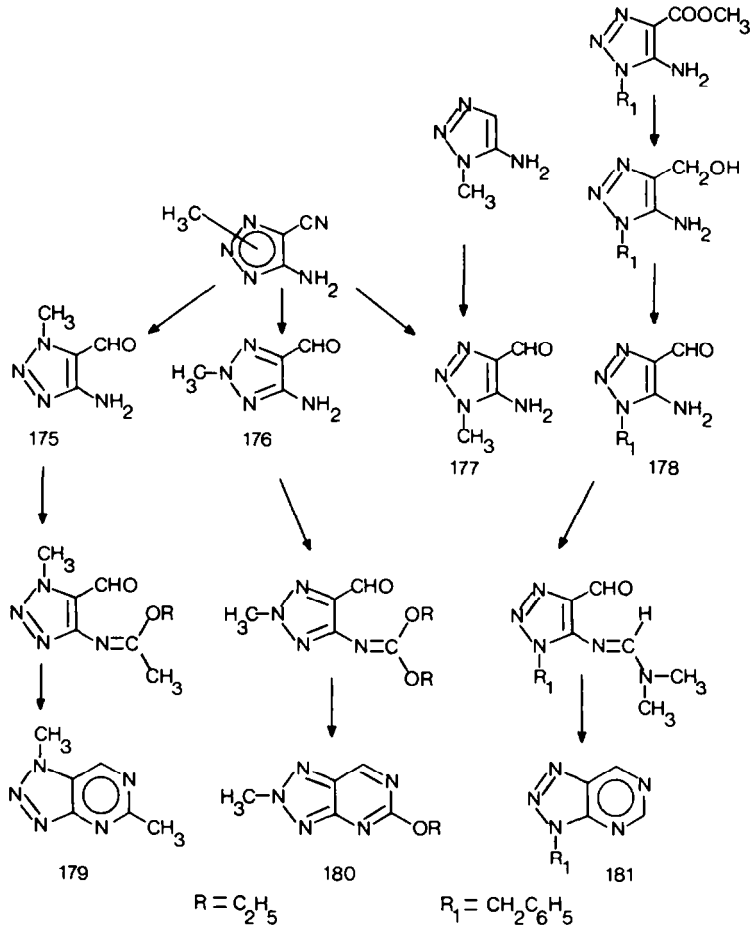
Introduction of the aminoaldehyde group in the pyrazole and isoxazole nucleus is possible via Vilsmeier-Haack formylation of appropriate amino derivatives (Scheme 18). Reaction of 5-amino-3-methyl-1-phenylpyrazole with phosphorus oxychloride in *N*,*N*-dimethylformamide gave 1-phenyl-3-methyl-5-aminopyrazole-4-carboxaldehyde **166** in 64% yield.[156] 3-Phenyl-5-aminoisoxazole-4-carboxaldehyde **167** was obtained similarly in 82% yield from 3-phenyl-5-aminoisoxazole.[157] Elaboration of the aminoaldehyde group in the pyrazole nucleus may also be accomplished via catalytic hydrogenolysis of the aminonitrile functionality, as illustrated for the synthesis of 1-methyl- and 1-phenyl-5-aminopyrazole-4-carboxaldehyde **172** in 27% and 72% yield, respectively.[158a] Acid-catalyzed condensations of **166** and ketones resulted in the pyrazolo[3,4-*b*]pyridine ring system, as shown for its reaction with cyclohexanone with formation of **168** (46%).[156] Acid-catalyzed and base-catalyzed condensations with **172** gave pyrazolo[3,4-*b*]pyridines, which were generally obtained in higher yields in the base-catalyzed process.[158b] Friedländer condensations of **167** with β-dicarbonyl

compounds gave isoxazolo[5,4-*b*]pyridines in moderate yield, illustrated for its reaction with malononitrile with formation of **170**.[157] The pyrazolo[3,4-*d*]pyrimidine **169** was obtained from **166** and formamide in 60% yield;[156] reaction of **167** and formamidine acetate resulted in the isoxazolo[5,4-*d*]pyrimidine **171** in 62% yield.[157] Treatment of aminoaldoximes, derived from **167** and **172**, with orthoformate gave *N*-oxides **173** and **174**, respectively (40%).



Scheme 18.

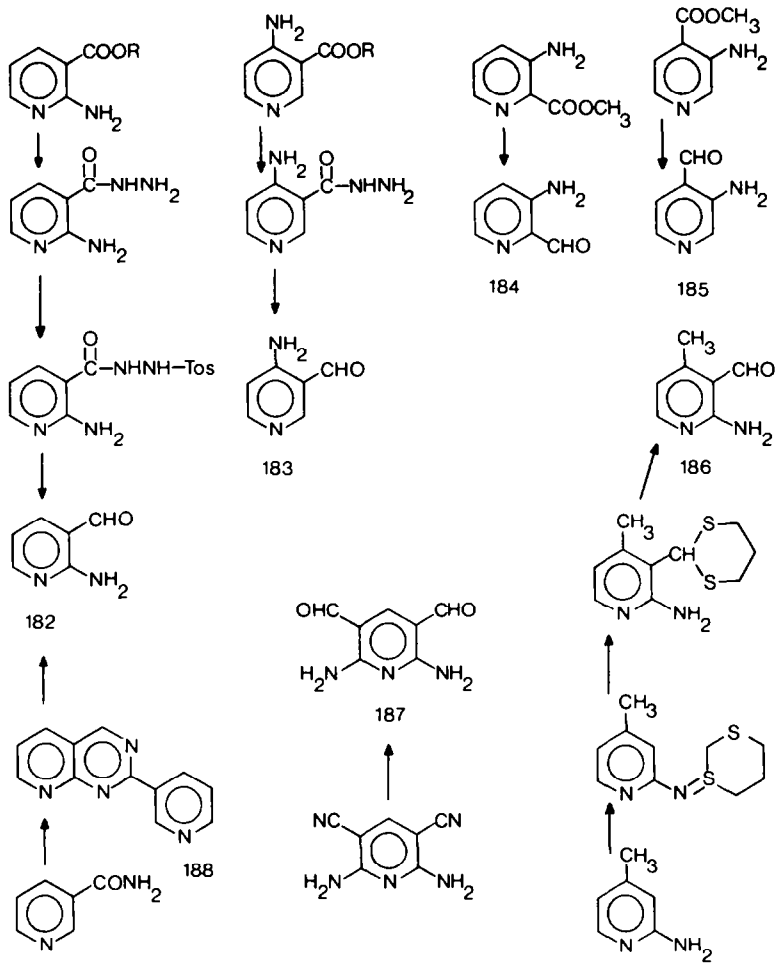
Aminotriazolecarboxaldehydes are attractive intermediates for the synthesis of 8-azapurines[159] (*v*-triazolo[4,5-*d*]pyrimidines), of interest in cancer research. Introduction of the aminoaldehyde functionality in the 1,2,3-triazole nucleus is best accomplished by functional group modification of corresponding aminocarboxylic acid derivatives (Scheme 19). Hydrogenolysis of 4-amino-5-cyano-1-(2- and 3-)methyl-1,2,3 triazoles with palladium in 0.1 M hydrochloric acid gave 4-amino-1,2,3-triazole-5-carboxaldehydes **175–177** in good to excellent yield[160] (the amino group is numbered 4 to facilitate comparison of the isomeric aminoaldehydes). The 3-benzyl derivative **178** could be prepared similarly. The *N*-unsubstituted aminoaldehyde was too unstable to be isolated. Aminoaldehydes **176** and **178** may also be obtained from the corresponding aminocarboxylic acid esters via reduction with lithium aluminum hydride, followed by oxidation of the aminohydroxymethyl group with manganese dioxide, as illustrated for the formation of **178**. Although the 1,2,3-triazole nucleus has the characteristics of a π-deficient heterocyclic system,[161] it was possible to effect direct 5-*C*-formylation of 4-amino-3-methyl-1,2,3-triazole to give **177** after hydrolysis of the intermediate 4-dimethylaminomethylene-5-carboxaldehyde.[162] 4-Amino-1-methyl-1,2,3,-triazole, on the other hand, could not be formylated in the triazole ring. The aminoaldehydes **175–178** are stable compounds even when dissolved in 0.1 M hydrochloric acid; self-condensation was, however, observed at higher acid strength.[160] They could not be acylated due to the very low nucleophilicity of the 4-amino group, and the conventional pyrimidine annelation could therefore not be carried out. Reaction with phosphorus



Scheme 19.

oxychloride and *N.N*-dimethylformamide, on the other hand, readily formed dimethylaminomethyleneamine aldehydes, which were readily cyclized to give substituted 8-azapurines. This sequence is illustrated by the formation of 9-benzyl-8-azapurine **181** starting from aminoaldehyde **178**.[163] Substituted 8-azapurines were also obtained from the aminoaldehydes via reaction with orthoesters and ring closure with ammonia. This is illustrated for the formation of 2,7-dimethyl-8-azapurine **179** from **175** and triethyl orthoacetate. Condensation with tetraethyl orthocarbonate followed by treatment with cold ethanolic ammonia gave 2-ethoxy-8-methyl-8-azapurine **180** starting from *o*-aminoaldehyde **176**.

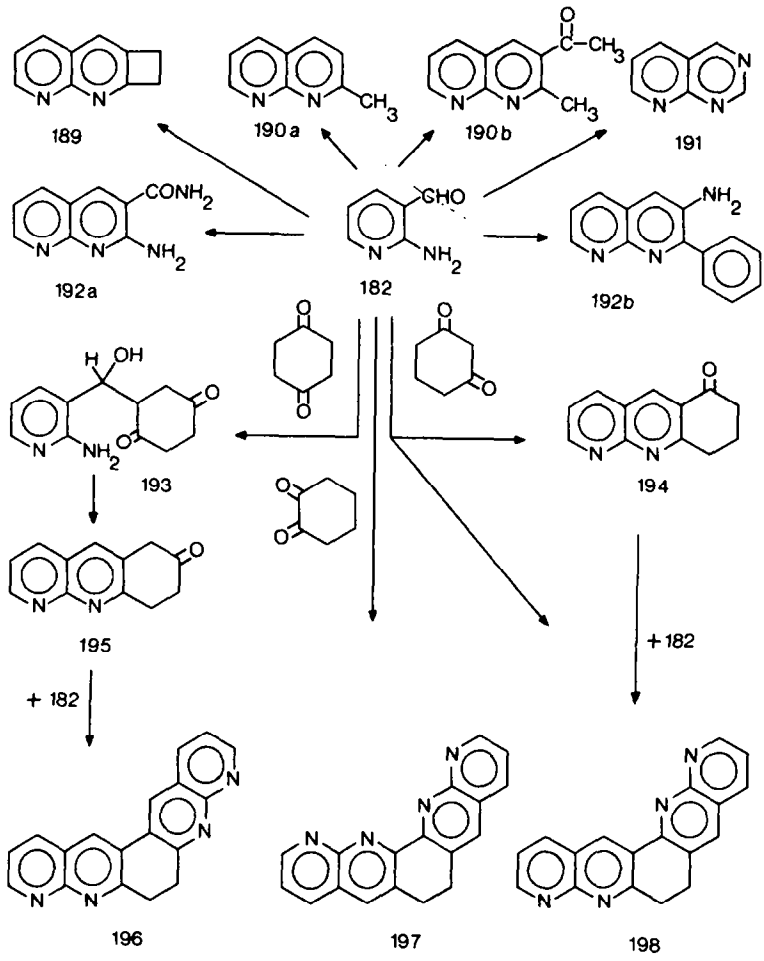
Introduction of the aminoaldehyde group in the pyridine nucleus can lead to four isomeric products: 2-aminonicotinaldehyde **182**, 4-aminonicotinaldehyde **183**, 3-aminopicolinaldehyde **184**, and 3-aminoisonicotinaldehyde **185**. These are generally accessible via functional group transformations of appropriate aminocarboxylic acid derivatives (Scheme 20). Application of the McFayden–Stevens procedure (see synthesis of **5**) to 2-aminonicotinic acid gave **182** in 51 % overall yield;[164,165] 6-phenyl-[165] and 4,6-dimethyl-2-aminonicotinaldehyde[166] were obtained similarly. In an alternative sequence, **182** was synthesized from 2-aminonicotinic acid by oxidative cleavage of the corresponding hydrazide with sodium metaperiodate.[167] Extension of this method to 4-aminonicotinic acid gave **183** in 10% yield, based on starting 3-picoline-1-oxide.[168,169] 3-Aminopicolinaldehyde **184** is not accessible via these synthetic methods;[164,167] it may be prepared, however, in excellent yield by metal hydride reduction of methyl 3-aminopicolinate[170] (no experimental details available). 3-Aminoisonicotinaldehyde **185** may be obtained similarly from methyl 3-aminoisonicotinate.[170,171] A more direct and convenient synthesis of 2-aminonicotinaldehyde **182** starts from nicotinamide.[172] Melt reaction with ammonium sulphamate produced pyrido[2,3-*d*]pyrimidine **188**,[173] which was readily hydrolyzed to give **182** together with nicotinic acid. This two-step process formally represents a remarkable transposition of the amide



Scheme 20.

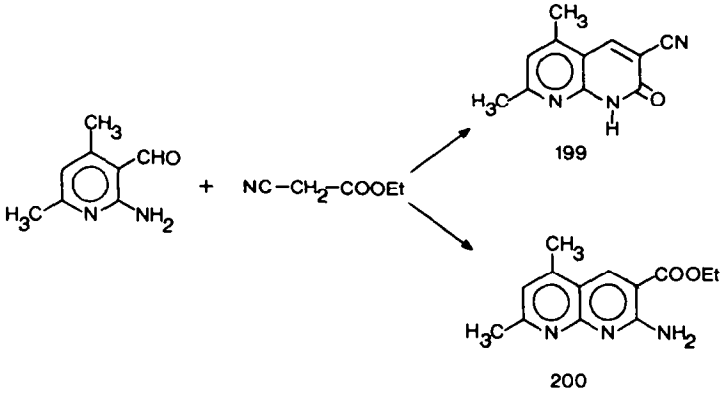
NH_2 group and the 2-hydrogen of the pyridine ring in nicotinamide. It will be noted that the amino and the aldehyde functionalities are generated simultaneously during the hydrolytic step, a process that may be extrapolated to substituted 2-aminonicotinaldehydes. Exploitation of this synthetic method for the heteroannelation of pyridine units will be discussed in detail in a further section. 2-Aminonicotinaldehydes may also be obtained from 2-aminopyridines by specific ortho-formylation via azasulphonium salts derived from the amines and dithian, as illustrated for the formation of 4-methyl-2-aminonicotinaldehyde **186**, or by oxidation of 2-amino-3-methylthiomethylpyridines.[174] These ortho-formylations of 2-aminopyridines are attractive synthetic alternatives when the aminocarboxylic acids or pyrido[2,3-*d*]pyrimidines (see below) are not readily available. Bis(aminoaldehyde) 2,6-diaminopyridine-3,5-dicarboxaldehyde **187** was obtained in good yield via hydrogenolysis of 2,6-diamino-3,5-dicyanopyridine.[175]

Aminoaldehydes **182–185** have been used mainly for the annelation of pyridine units, and their reactions with activated methylene compounds provide a general synthetic entry into 1,8-, 1,6-, 1,5-, and 1,7-naphthyridines. Friedländer condensations of **182** and ketones lead to 2- and 2,3-disubstituted 1,8-naphthyridines, as illustrated in Scheme 21 by the piperidine catalyzed condensation with acetone and acetylacetone with formation of **190a** and **190b** (90%)[165] and by the acid-catalyzed condensation with cyclobutanone leading to **189**.[176] Condensation of **182** and 1,3-cyclohexanedione gave tricyclic ketone **194** or pentacyclic **198**, depending on the molar ratio of the reactants; **194** could be readily transformed into **198** upon further reaction with **182**.[177] 1,4-Cyclohexanedione and **182**, in the presence of piperidine, gave the non-cyclized aldol product **193**, a clear demonstration that under these conditions aldol condensation is the first step in Friedländer condensations with **182**. Treatment of **193** with boiling toluene readily gave the ring closed ketone **195**, which could be further condensed with **182** in refluxing toluene to give **196** in excellent yield.[177] Base-

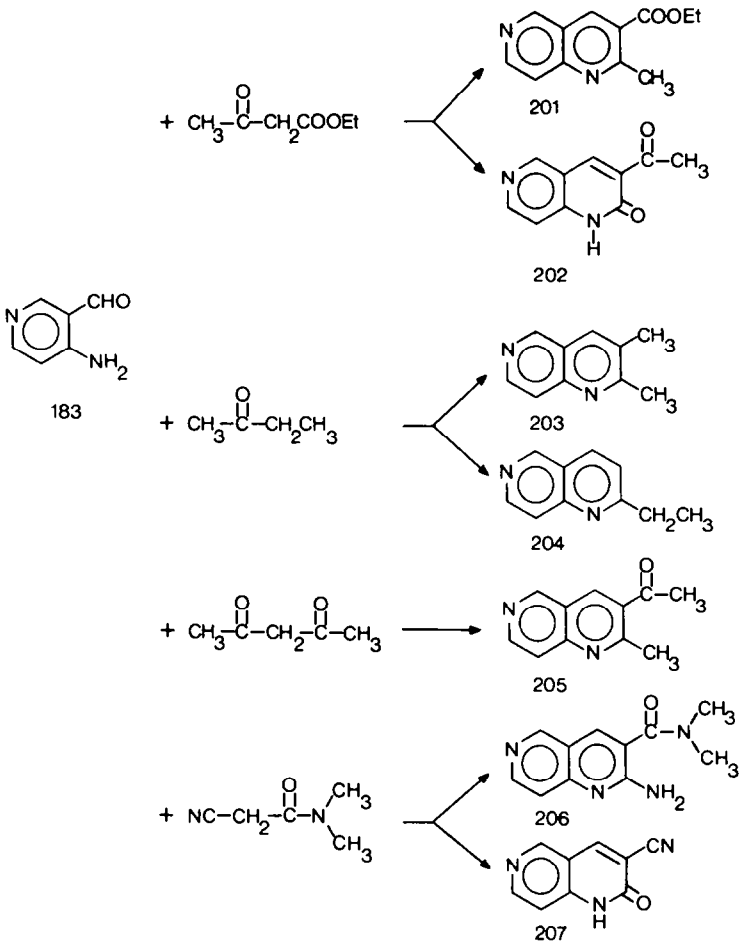


Scheme 21.

catalyzed condensations of **182**, and 1,2-cyclohexanedione gave the bis-condensation product **197** in moderate yield; a monocondensation product was not isolated in this reaction.[177] Condensation reactions of **182** with malonic acid derivatives and similarly activated methylene compounds may be illustrated by the formation of 2-amino-1,8-naphthyridine-3-carboxamide **192a**[178] and 3-amino-2-phenyl-1,8-naphthyridine **192b**[165] from cyanoacetamide and phenylacetonitrile, respectively. Reactions of 4,6-dimethyl-2-aminonicotinaldehyde and cyanoacetates are dependent on the condensation catalyst.[179] In the piperidine catalyzed condensation 3-cyanonaphthyridone **199** was obtained, the result of ring closure with the ester group of the cyanoacetate; with zinc chloride, on the other hand, aminoester **200** was formed in 77% yield, together with **199** (22%) (eqn 37). Ring



eqn 37

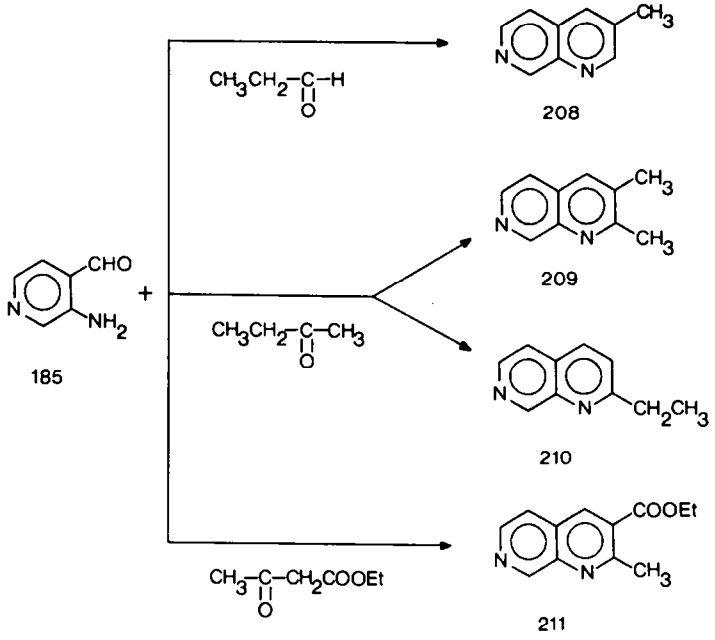


Scheme 22.

formation via attack on the nitrile group is facilitated by its coordination with the metal ion, which greatly increases its electrophilic character. Pyrido[2,3-*d*]pyrimidine **191** is available from **182** by formylation with acetic formic anhydride followed by treatment with methanolic ammonia.[168]

Friedländer condensations of 4-aminonicotinaldehyde **183** and ketomethylenes possessing two potential reactive sites deviate substantially from those described earlier for *o*-aminobenzaldehyde and 2-aminonicotinaldehyde. It was found that the outcome of such reactions was often critically dependent on the base catalyst employed in condensations with **183** (Scheme 22).[180] Reaction with ethyl acetoacetate catalyzed by sodium hydroxide gave ethyl 2-methyl-1,6-naphthyridine-3-carboxylate **201**, the result of the expected ring closure with the ketone functionality. The piperidine catalyzed condensation, on the other hand, gave a 1:1 mixture of **201** and 3-acetyl-1,6-naphthyridine-2(1H)one **202**, the latter arising from cyclization with the ester group of the ketomethylene. The analogous piperidine catalyzed condensation with 2-aminonicotinaldehyde gave only the product derived from ring closure with the ketone group[165] and, as shown earlier, *o*-aminobenzaldehyde gave 2-methyl-3-carboethoxyquinoline in a base catalyzed reaction; ring closure with the ester group was only observed at high temperature in the absence of catalysts (see eqn 26). Friedländer condensation of **183** and methyl ethyl ketone in the presence of piperidine gave nearly identical amounts of 2,3-dimethyl-1,6-naphthyridine **203** and 2-ethyl-1,6-naphthyridine **204**; the sodium hydroxide catalyzed reaction gave only the 2,3-dimethyl derivative **203**, the anticipated product by analogy with the reaction of *o*-aminobenzaldehyde (see Scheme 9). Only one product was obtained in the reaction of **183** and acetylacetone, identified as 2-methyl-3-acetyl-1,6-naphthyridine **205**. Condensation of **183** with *N*,*N*-dimethylcyanoacetamide in the presence of sodium hydroxide gave the anticipated disubstituted aminoamide **206**; the piperidine catalyzed condensation on the other hand resulted in the elimination of *N*,*N*-dimethylamine with formation of 3-cyano-1,6-naphthyridine-2(1*H*)one **207**. The detailed sequence of elementary steps in Friedländer condensations in general, and for **183**

specifically, are not known (see above). It was suggested that in reactions of **183** with ketones Schiff base formation would be the initial step in the condensation,[180] and that in its reaction with substituted acetonitriles aldol condensation would initiate ring formation.[169] It is conceivable that a delicate electrophilic-nucleophilic balance of the aldehyde and amino functionalities exist in **183**, which could be easily shifted by the coreactive partner and/or the catalyst employed in their condensation. It is known, however, that the reaction product of less complex aldehydes (e.g. benzaldehyde) and unsymmetrical ketones is occasionally different in their piperidine catalyzed condensation (Knoevenagel reaction) from that in the metal hydroxide promoted Claisen–Schmidt reaction.[182] It is not clear why this would result in different products in condensations with **183** and not with the related **182**. Condensation reactions of **183** with substituted acetonitriles and malononitrile derivatives lead to 3-substituted 2-amino-1,6-naphthyridines, of which a large number have been prepared.[169,182]

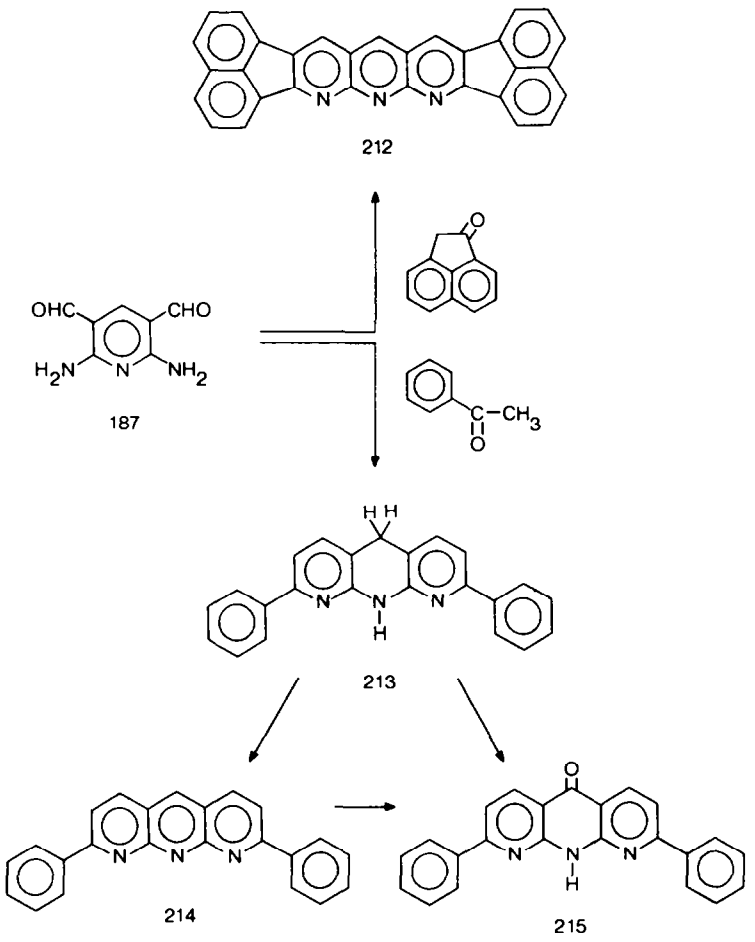


eqn 38

Very few condensation reactions with 3-aminopicolinaldehyde **184** have been described. Its reactions with ethyl acetoacetate, acetylacetone and diethyl malonate lead to 1,5-naphthyridines; condensation with malononitrile, on the other hand, did not result in the formation of the anticipated 2-amino-3-cyano-1,5-naphthyridine.[170]

Friedländer condensation of 3-aminoisonicotinaldehyde **185** and propionaldehyde, catalyzed by sodium hydroxide, gave 3-methyl-1,7-naphthyridine **208** in 60% yield[171] (eqn 38). This reaction is a rare example of the successful use of aliphatic aldehydes in base-catalyzed condensations with aminoaldehydes. As discussed earlier, the similar condensation with *o*-aminobenzaldehyde did not result in 3-methylquinoline. The sodium hydroxide catalyzed condensation of **185** and methyl ethyl ketone gave a mixture of two products, composed of 90% 2,3-dimethyl-1,7-naphthyridine **209** and 10% 2-ethyl-1,7-naphthyridine **210**.[171] It will be noted that under these conditions only one product (**203**) was obtained from the isomeric **183** (see above). Ethyl acetoacetate and **185** gave the normal condensation product **211** exclusively.[170] The synthesis of the 1,7-naphthyridine nucleus has also been accomplished by the Borsche condensation of the anil derivative of **185**.[183]

Annelation reactions of 2,6-diaminopyridine-3,5-dicarboxaldehyde **187** and ketones provide entry into the 1,9,10-anthyridine system (eqn 39).[175] Base catalyzed condensation of **187** and acenaphthenone gave the polycondensed linearly annelated ring system **212** in 65% yield. Condensations with other ketones (e.g. acetophenone, α-tetralone, deoxybenzoin) are more complex and result in the formation of reduced anthyridines, rather than the expected fully aromatic heterocycle. Thus, acetophenone and **187** gave the insoluble dihydroanthyridine **213**, which could be oxidized to the fully aromatic 2,7-diphenyl-1,9,10-anthyridine **214** or to the anthyridone **215** depending on the contact time with the oxidating agent. The unusual formation of a reduced annelation product in

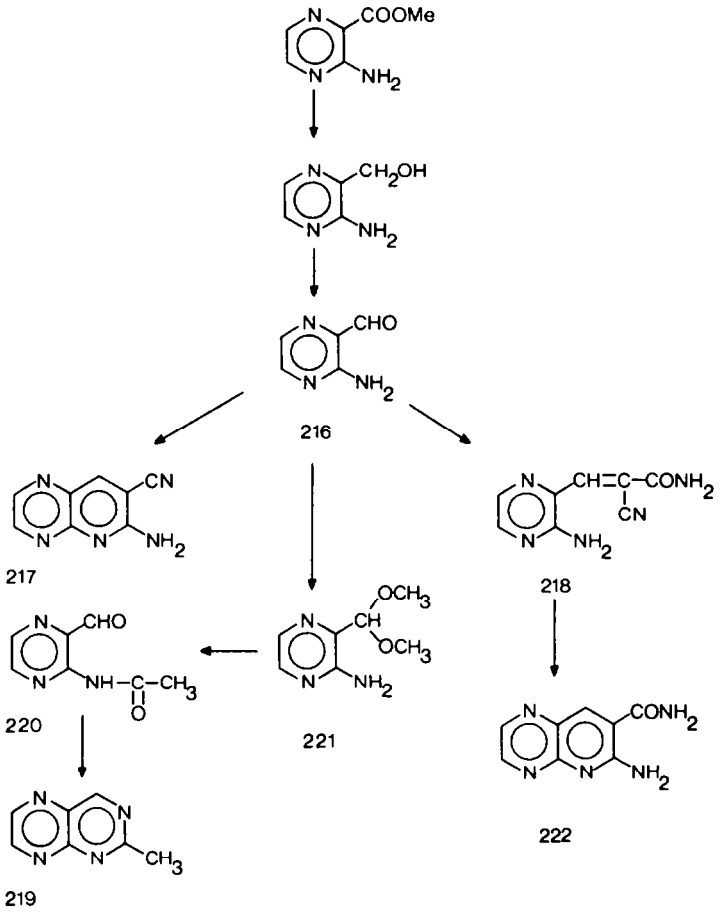


eqn 39

condensations with **187** was shown to be the result of hydride transfer from the solvent to the anthyridine moiety initially formed in the reaction medium. The direct formation of **212** is the result of its insolubility under the reaction conditions, which greatly retards the hydride transfer reaction.

3-Aminopyrazine-2-carboxaldehyde **216** is of interest for the synthesis of 4-unsubstituted pteridines. This aminoaldehyde may be prepared conveniently from methyl 3-aminopyrazine-carboxylate;[184] reduction of the ester group with lithium aluminum hydride gave 2-amino-3-hydroxymethylpyrazine, which was readily oxidized with manganese dioxide to give **216** (eqn 40). It is also obtained from pteridine by acid hydrolysis,[185] a reaction of little synthetic value. Reduction of 2-amino-3-cyanopyrazine did not result in the formation of **216**.[184] This aminoaldehyde is resistant to acylation with acid chlorides or anhydrides[184] but could be formylated with the Vilsmeier-Haack reagent.[186] It was possible to obtain acylated derivatives of **216** via the reaction of acetal **221**, obtained from **216** and boron trifluoride-methanol, and acid chlorides, as illustrated for the synthesis of 3-acetamidopyrazine-2-carboxaldehyde **220**. Treatment with ethanolic ammonia converted the latter into 2-methylpteridine **219** in 34% yield.[184] Pteridine-2-one was obtained by a similar sequence in 55% yield. This pteridine synthesis is, however, not very satisfactory for the parent compound or for ethyl pteridine-2-carboxylate. Condensation of **216** with malononitrile gave **217** (47%); the reaction with cyanoacetamide gave **218**, which was readily cyclized by base to give **222** (63%).[187]

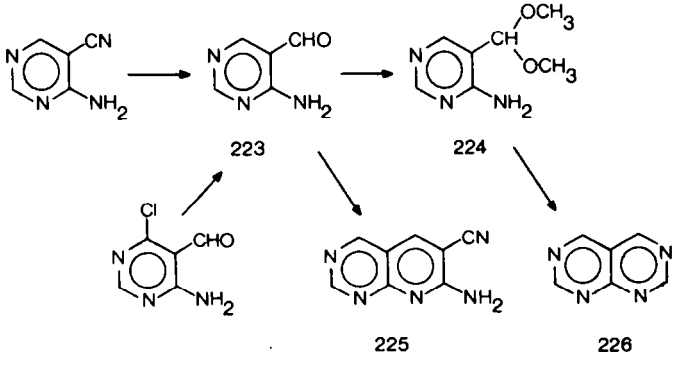
Reduction of 4-amino-5-cyanopyrimidines in acid medium provides a convenient synthesis for 4-aminopyrimidine-5-carboxaldehyde **223** and its 2-substituted derivatives (eqn 41).[188,189] These are also accessible via catalytic hydrogenation of 4-amino-6-chloropyrimidine-5-carboxaldehydes in the presence of magnesium oxide.[190] Formylation of 1,3-dimethyl-4-aminouracil with formic acetic anhydride[191] or with *N*,*N*-dimethylformamide-phosphorus oxychloride[192] gave aminoaldehyde **227**. Conversion of **223** into pyrimido[4,5-*d*]pyrimidine **226** by conventional annelation methods was not successful because the highly reactive fused pyrimidine ring system was hydrolyzed by water, formed during such ring closing reactions. Conversion of **223** into the acetal **224** followed by reaction

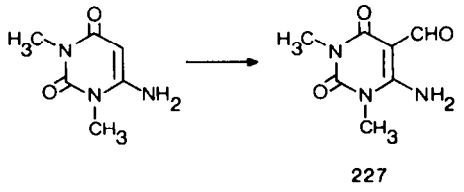


eqn 40

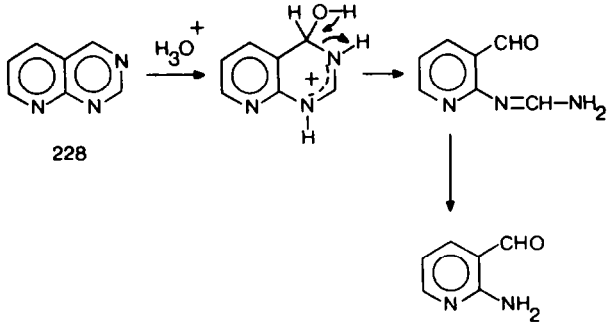
with *s*-triazine, under rigorously anhydrous conditions, permitted the isolation of **226** in 20% yield.[190] Condensations of **223** with malonic acid derivatives are illustrated for its reaction with malononitrile with formation of **225** in 86% yield.[193] Friedländer condensations of **223** and ketones lead to pyrido [2,3-*d*]pyrimidines; these will be discussed in detail in a later section.

The four possible pyridine ring substituted quinoline aminoaldehydes have been mentioned in the literature without experimental details.[194a,b] Two of these, 3-aminoquinoline-4-carboxaldehyde and





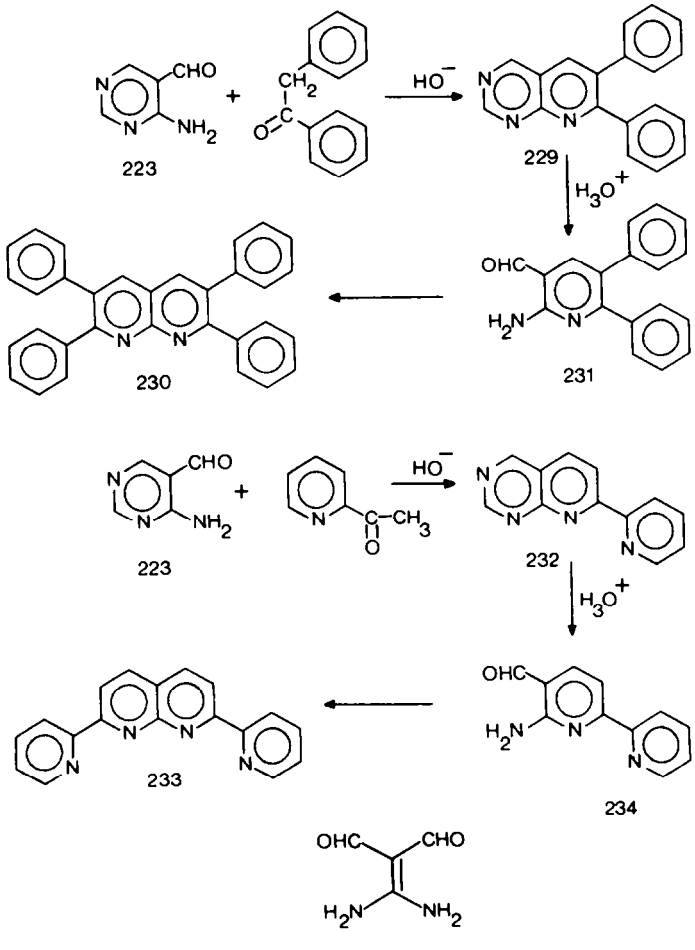
eqn 41



eqn 42

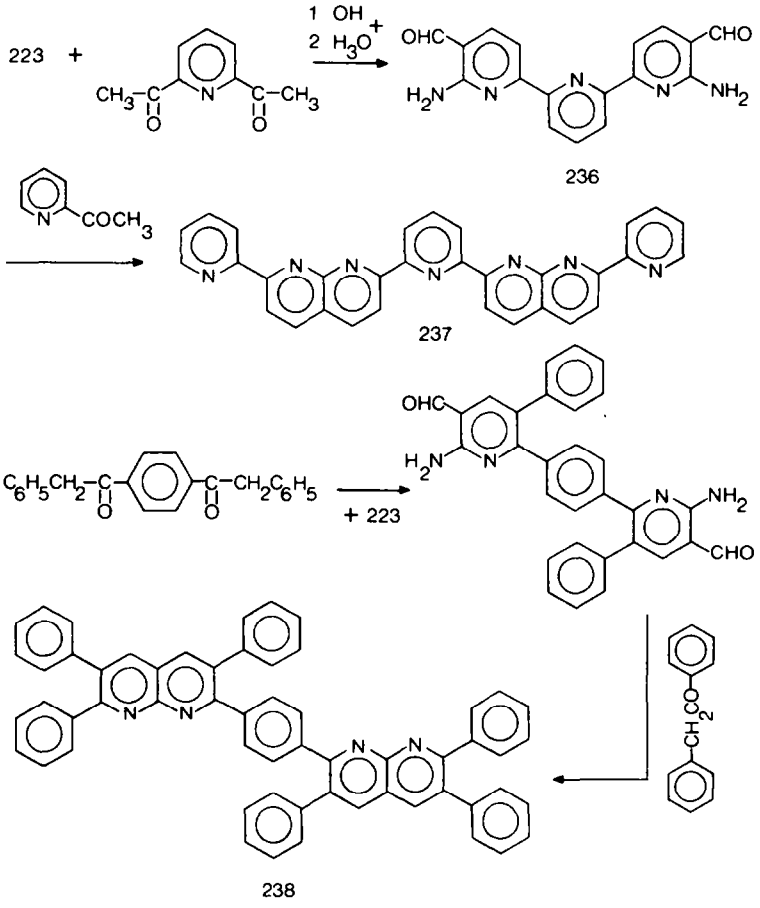
4-aminoquinoline-3-carboxaldehyde were condensed with ketones and substituted acetonitriles with formation of benzo [*f*]1,7-naphthyridines and benzo[*h*]1,6-naphthyridines, respectively.[194]

The successful synthesis of heterocyclic aminoaldehydes depends to a large extent on the availability of aminocarboxylic acid derivatives as precursors for the required functional group transformations. Their use in the McFayden–Stevens synthesis generally involves lengthy procedures; reduction of aminonitriles may be complicated by simultaneous reduction of the heterocyclic ring system.[175] These synthetic methods are, therefore, not very attractive for the elaboration of polycyclic, heterocyclic aminoaldehydes. An entirely different strategy for their synthesis is suggested by the facile acid-catalyzed ring opening of pyrido[2,3-*d*]pyrimidine **228** with formation of 2-aminonicotinaldehyde **182**.[168,172] The driving force for this transformation is the acid-catalyzed

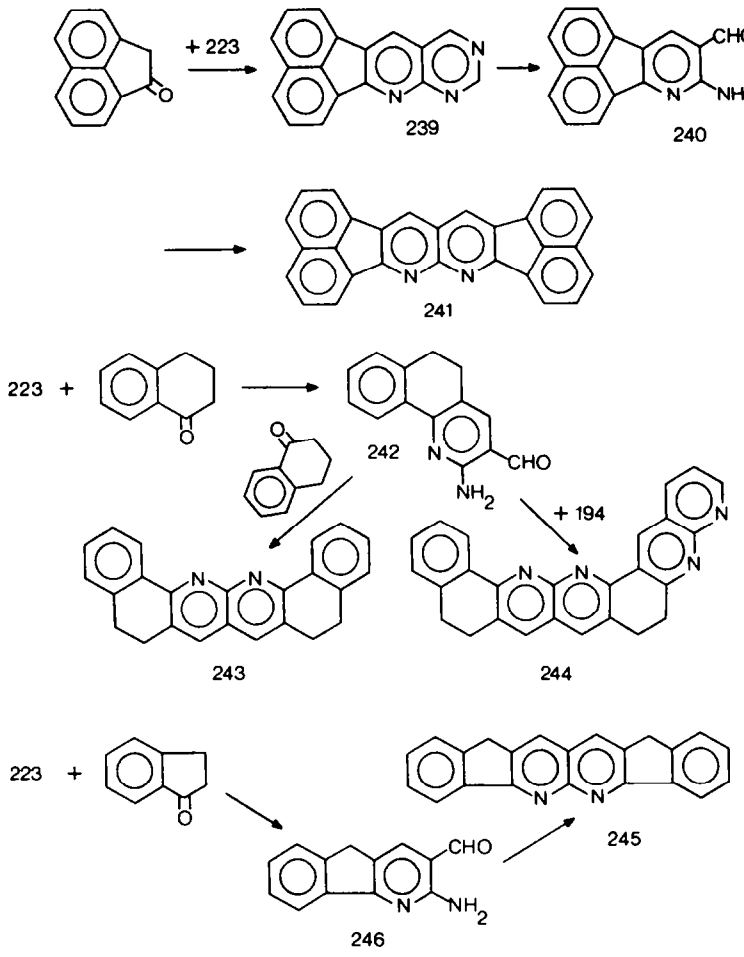


Scheme 23.

covalent hydration[195] of this heterocycle, followed by irreversible ring opening of the pyrimidine moiety of **228** (eqn 42). Exploitation of this hydrolytic reaction for the synthesis of *N*-heterocyclic aminoaldehydes requires a versatile synthesis of pyridine-substituted and pyridine-fused pyrido[2,3-*d*]pyrimidines. This may be accomplished by the Friedländer condensation of 4-aminopyrimidine-5-carboxaldehyde **223**. Base-catalyzed condensation of **223** and deoxybenzoin gave 6,7-diphenylpyrido[2,3-*d*]pyrimidine **229** in 75% yield; condensation with 2-acetylpyridine similarly resulted in 7-(2-pyridyl)-pyrido[2,3-*d*]pyrimidine **232** in 85% yield.[196] This condensation reaction appears general for aromatic ketones; simple aliphatic ketones (acetone, cyclohexanone) did not yield the pyrido [2,3-*d*]pyrimidine system. Acid-catalyzed ring opening of the pyrimidine moieties of **229** and **232** gave 5,6-diphenyl-2-aminonicotinaldehyde **231** and 6-(2-pyridyl)-2-aminonicotinaldehyde **234** in nearly quantitative yield.[196] Recondensation of **231** with deoxybenzoin and of **234** with 2-acetylpyridine gave 2,3,6,7-tetraphenyl-1,8-naphthyridine **230**[175] and 2,7-di(2-pyridyl)-1,8-naphthyridine **233** in very high yield[197] (Scheme 23). Analysis of the conversion of **223** into **230** and **233** reveals the attractive features of this heteroannelation sequence. The conversion of **223** into **234** corresponds to a transformation of the pyrimidine moiety of **223** into a pyridine unit (**234**), while preserving the aminoaldehyde functionality in the same relative position. Furthermore, this interconversion of heterocyclic rings is accompanied by the introduction of a substituent, the 2-pyridyl group of **234** derived directly from the starting ketone. If one considers the conversion of 2-acetylpyridine into **234**, then it is seen that the acetyl group of the former is transformed into a 2-aminopyridine-3-carboxaldehyde fragment linked at the 6-position with the ketonic residue. One can also consider the transformation **223** → **233**. From this point of view it is seen that 4-aminopyrimidine-5-carboxaldehyde is employed as synthon for the unknown diaminomethylene malonaldehyde **235** in its reaction with ketones. It should be emphasized that the two individual steps (base catalyzed **223** → **232** and acid catalyzed **232** → **234**) remain separate, so that premature condensation of the starting ketone and the newly generated aminoaldehyde is not possible. This feature is important when



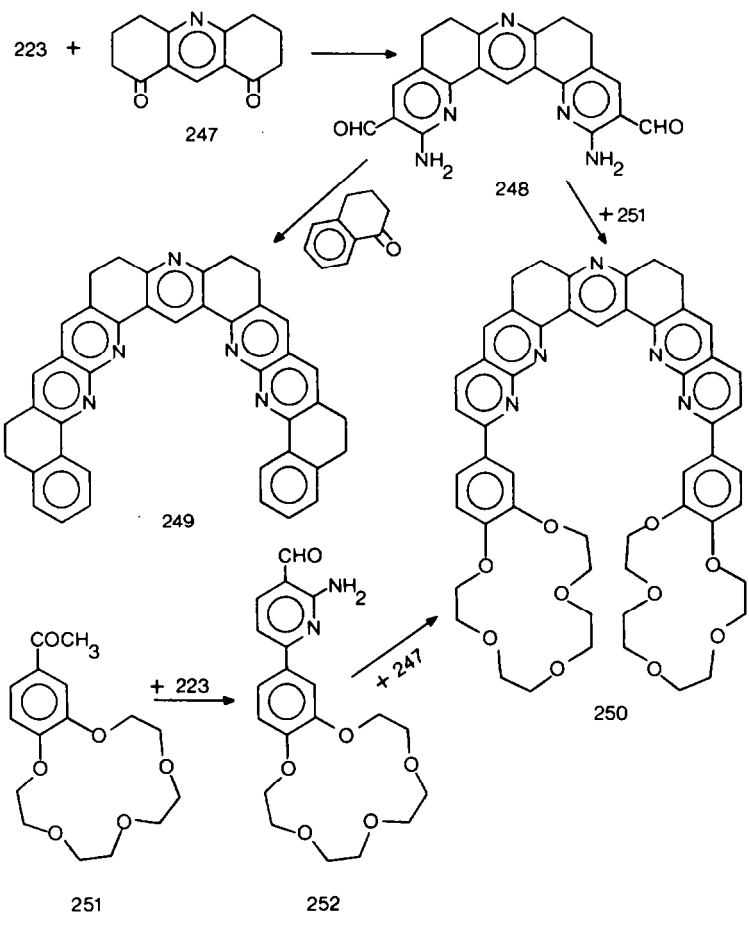
Scheme 24.



Scheme 25.

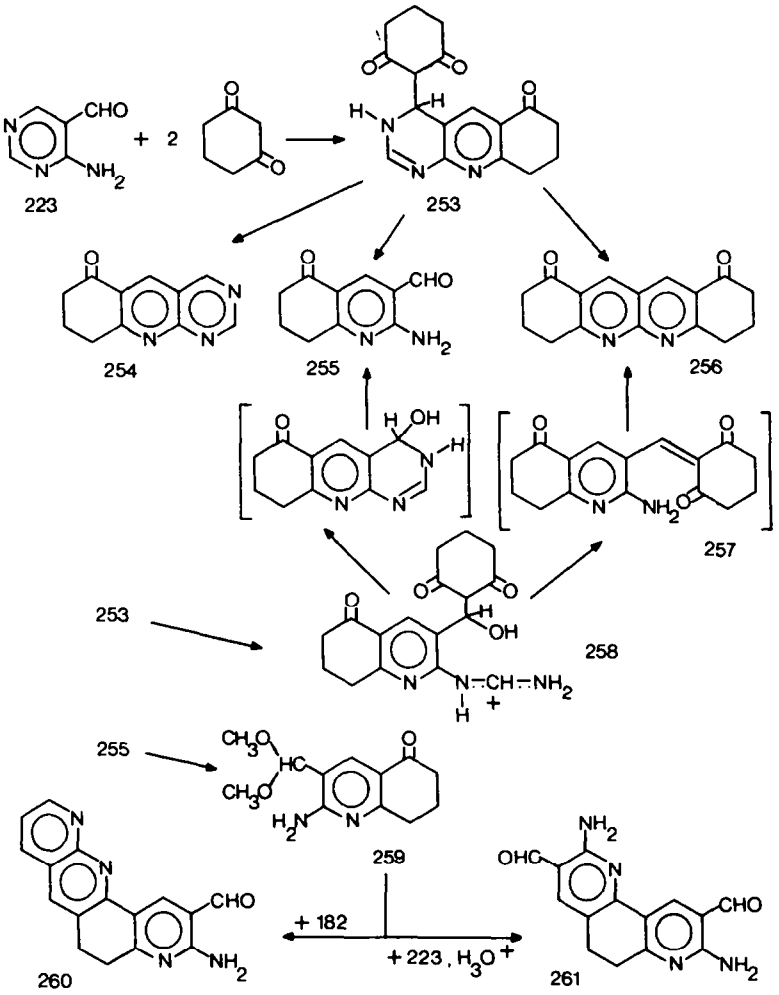
unsymmetrical systems are considered. It is noteworthy that the formation of **234** provides a facile entry into the 2,2-bipyridine system. Extension of this sequence to 2,6-diacetylpyridine readily gave the terpyridine bis(aminoaldehyde) **236**, which was condensed with 2-acetylpyridine to give heptacyclic **237**, composed exclusively with pyridine rings.[197] Polyphenylated 1,8-naphthyridine **238** was obtained by an analogous sequence (Scheme 24).

Polycyclic systems containing a fused terminal pyrido[2,3-*d*]pyrimidine moiety are easily obtained by Friedländer condensation of **223** with cyclic ketones (Scheme 25). Base-catalyzed condensation of **223** with acenaphthenone gave acenaphtho[1′,2′:5,6]pyrido-[2,3-*d*]pyrimidine **239** in 95% yield. Hydrolytic cleavage of the pyrimidine moiety resulted in the formation of 8-aminoacenaphtho[1,2-*b*]pyridine-9-carboxaldehyde **240** in nearly quantitative yield. This aminoaldehyde was further condensed with acenaphthenone to give diacenaphtho[1,2-*b*:1′,2′-*g*]1,8-naphthyridine **241** (100%).[198] When α-tetralone[198] and 1-indanone[199] were employed in a similar sequence, fused polycondensed systems **243** and **245** were obtained in high yield. The formation of an unsymmetrical polycondensed system **244**, derived from successive Friedländer condensations of α-tetralone and **194**, is also illustrated. The ready availability and wide choice of cyclic ketones, the ease of operation and the high yields obtained make this heteroannelation sequence a versatile tool for the construction of multiple, fused ring structures. The aminoaldehydes obtained in these condensation-hydrolysis sequences, e.g. **240**, **242** and **246** may, of course, also be used for different annelation purposes. The use of cyclic diketones allows the rapid buildup of large polycyclic ring assemblies, as illustrated for the condensation/hydrolysis sequence of **223** and 1,8-dioxooctahydroacridine **247**, which resulted in bis(aminoaldehyde) **248**. Recondensation of the latter with α-tetralone gave the undecacylic heterocyclic system **249**;[199] condensation with 4-acetylbenzocrown-5 **251** led to the heterocyclic bis-crown ether **250**, which was also obtained via condensation/hydrolysis of **251** and **223** to give aminoaldehyde **252**, followed by condensation with **247**[200] (Scheme 26).

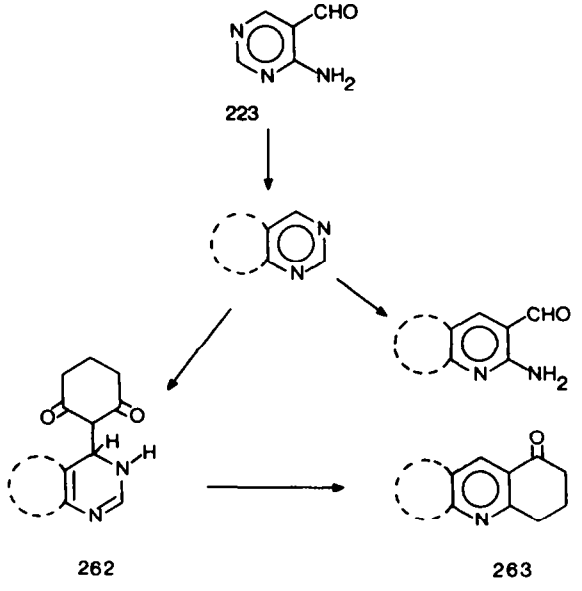


Scheme 26.

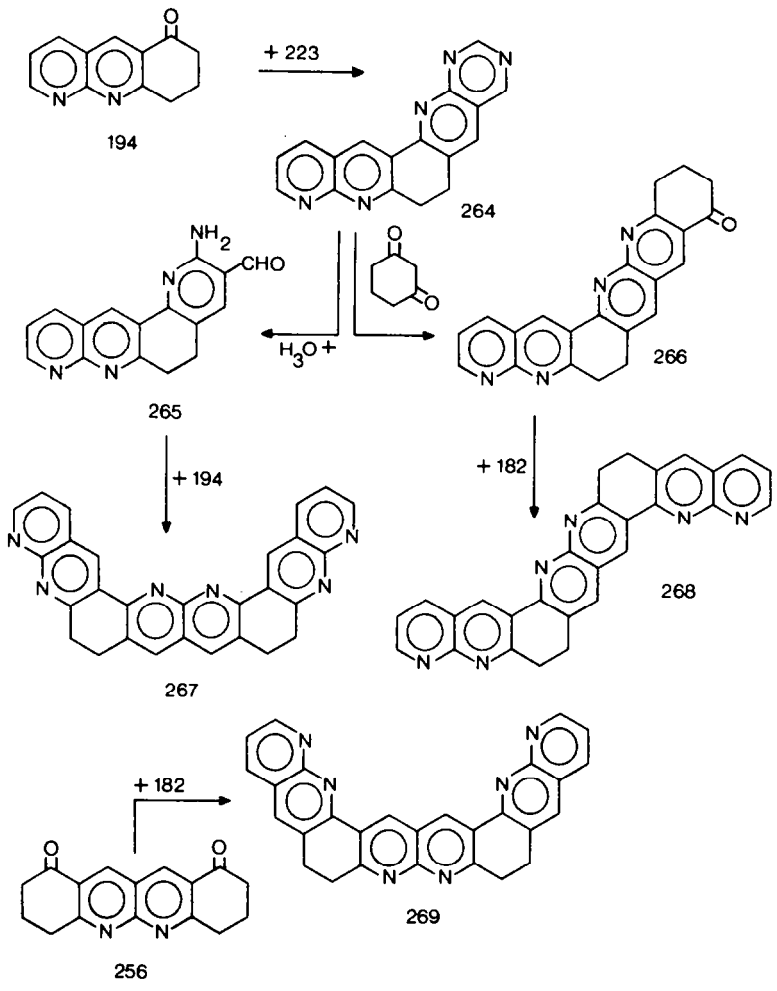
The presence of a fully aromatic pyrido[2,3-*d*]pyrimidine moiety is not a necessary condition for a successful transformation into aminoaldehydes. This was observed during a study of the reaction of **223** and 1,3-cyclohexanedione[201] (Scheme 27). An ethanolic solution of the components in the absence of catalyst, gave a quantitative yield of the addition product **253**, formed from one mole of **223** and two moles of the 1,3-dione. Its formation may be visualized as the result of nucleophilic addition of 1,3-cyclohexanedione on the fused pyrimidine moiety of **254**, initially forming during the condensation reaction. Treatment of the dihydropyrido[2,3-*d*]pyrimidine **253** with dilute acid gave 2-amino-5-oxo-5,6,7,8-tetrahydroquinoline-3-carboxaldehyde **255** in 70% yield; when **253** was boiled briefly with 2N HCl 1,10-dioxo-1,2,3,4,7,8,9,10-octahydrodibenzo[*b*,*g*]1,8-naphthyridine **256** was obtained (90%). Pyrolysis of **253** at 170° gave **254** and 1,3-cyclohexanedione, which were difficult to separate due to the very high reactivity of the electron deficient **254** towards nucleophiles. The key element in the transformation **253** → **255**, **256** is the loss of the 1,3 -dione moiety at intermediate pH and its incorporation in the final product (**256**) at low pH. Thus, protonation of **253** and subsequent hydrolytic cleavage results in the formation of *N*-substituted formamidinium ion **258**. At low pH dehydration of the β-hydroxy ketone moiety leads to the formation of α,β-unsaturated ketone **257**, after hydrolysis of the formamidine system. At intermediate pH a free terminal amine of the amidine is available for nucleophilic displacement of the 1,3-cyclohexanedione moiety. Further hydrolysis of the newly formed pyrimidine nucleus leads then to *o*-aminoaldehyde **255**. The formation of tetracyclic **256** from monocyclic starting materials represents a remarkably efficient heteroannelation reaction. The presence of the coreactive aminoaldehyde and ketone functionalities in **255** offers unique possibilities for heteroannelation reactions, wherein the *o*-aminoaldehyde group may be transferred directly into a polycyclic system. This annelation sequence may be illustrated by the formation of *o*-aminoaldehyde **260** and bis-(aminoaldehyde) **261** via condensations with the acetal **259**, derived from **255** and methanolic hydrochloric acid, and 2-aminonicotinaldehyde **182** and 4-aminopyrimidine-5-carboxaldehyde, respectively[202] (Scheme 27).



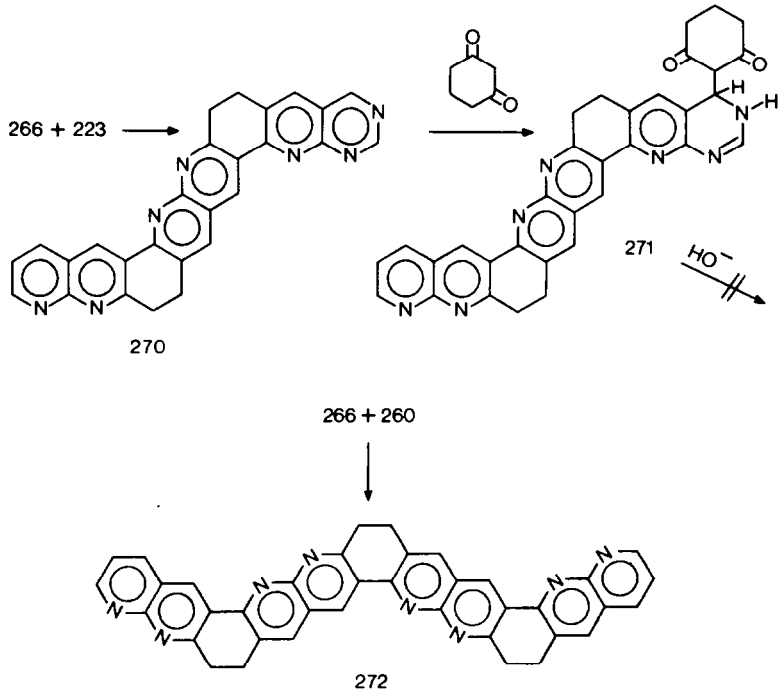
Scheme 27.



eqn 43

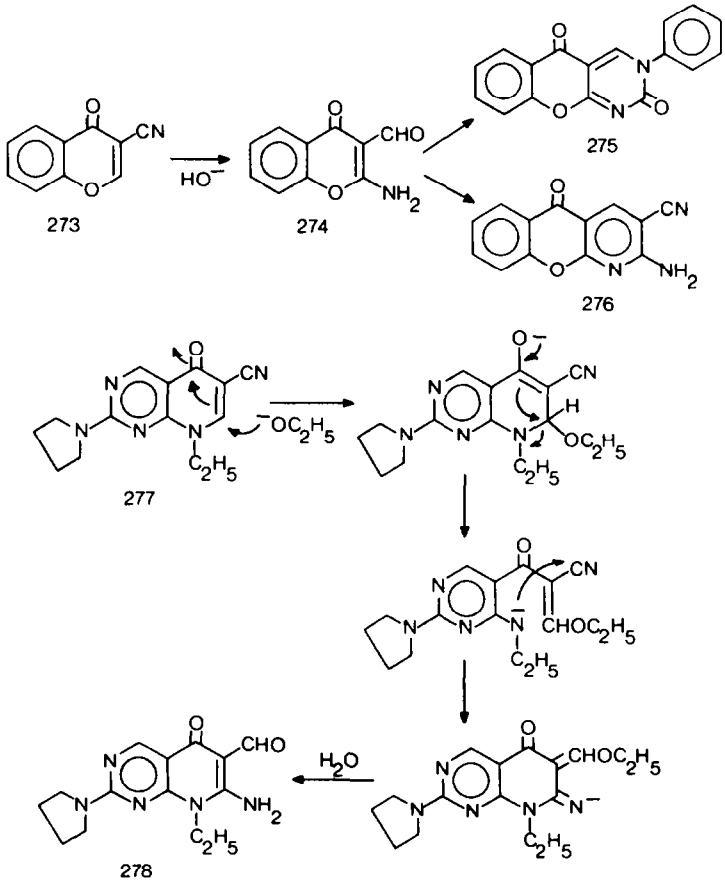


Scheme 28.



Scheme 29.

The scope of heteroannelations with 4-aminopyrimidine-5-carboxaldehyde may be further expanded by reacting its Friedländer condensation products with 1,3-cyclohexanedione.[203] Nucleophilic addition of the 1,3-dione on an electron deficient fused pyrimidine moiety gives **262**, which may be transformed with base into the annelated ketone **263**, containing an additional six-membered ring fused to a pyridine nucleus (eqn 43). Such transformations are well documented for several heterocyclic systems fused to a pyrimidine moiety.[187,204] It is thus possible to generate the coreactive aminoaldehyde and ketone functionalities from a single starting material, which itself is obtained from the same functional groups.[203] The combination of these complementary heteroannelations forms the basis of our recently described regioselective angular annelation reaction leading to the isomeric octacyclic heterocycles **267**, **268** and **269**, which differ only in the direction of angular ring fusion[203] (Scheme 28). Reaction of 2-aminonicotinaldehyde **182** and 1,3-cyclohexanedione in a 1:1 molar ratio gave naphthyridine ketone **194** (see above). Friedländer condensation of this ketone with 4-aminopyrimidine-5-carboxaldehyde **223** resulted in the formation of the fused pyrimidine **264** (60%), which was readily hydrolyzed to the tetracyclic aminoaldehyde **265**. Recondensation of the latter with **194** gave octacyclic fused ring structure **267** in 90% yield. Fused pyrimidine **264** and 1,3-cyclohexanedione resulted in the formation of the annelated cyclic ketone **266** in nearly quantitative yield, upon treatment of the primary addition product with base. Condensation of **266** with 2-aminonicotinaldehyde **182** formed the zig–zag shaped octacyclic **268** in 88% yield. These two heteroannelation methods result in the fusion of identical ring segments in angular directions that differ by 120°. A third octacyclic isomer **269** is accessible via the condensation of 4-aminopyrimidine-5-carboxaldehyde and 1,3-cyclohexanedione, from which diketone **256** may be obtained in high yield (see above). Its condensation with **182** resulted in the formation of **269** in low yield. Inspection of the synthetic sequences employed for the elaboration of the three isomeric octacyclic compounds **267**, **268** and **269** reveals that they are obtained from identical starting materials in the same relative proportions. Their order of introduction determines, in an absolute way, the stereochemical outcome



Scheme 30.

of the successive ring annelations. Aminoaldehyde **265** (obtained from 1,3-cyclohexanedione, **182** and **223**) is isomeric with **260**, derived from the same starting materials.

The heteroannelation sequence employed for the synthesis of **268** may in principle be repeated starting from hexacyclic ketone **266** (Scheme 29). Friedländer condensation of **266** and **223** gave the fused pyrimidine **270** in excellent yield. Nucleophilic addition of 1,3-cyclohexanedione proceeded readily with formation of **271**. Its transformation into the annelated ketone by treatment with base was, however, not successful, and starting **271** was recovered unchanged.[202] The failure of this ketone annelation reaction is due to the extreme insolubility of the addition product **271** in base-compatible solvents. A successful repetitive annelation sequence was found starting from 4-aminopyrimidine-5-carboxaldehyde via its transformation into aminoaldehyde **255**, from which **260** is readily obtained (see above). Condensation of the latter with cyclic ketone **266** gave the undecacyclic **272**, which represents the next higher homolog in the series **198** → **268** → **272**.[202]

The base-initiated conversions of 3-cyanochromone **273** into 2-amino-chromone-3-carboxaldehyde **274**[205] and of nitrile **277** into aminoaldehyde **278**[206] exemplify a different strategy for the one-step elaboration of the aminoaldehyde functionality (Scheme 30). These transformations are the result of a ring opening-ring closure reaction sequence as shown for the conversion of **277** → **278**. Annelation of **274** with phenyl isocyanate gave **275** in 36% yield; condensation with malononitrile resulted in **276** in 42% yield.[205]

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